ABU DEIAB, GHINA'A I., Ph.D. Synthesis and Biological Evaluation of Potent Neuroprotective Agents against Stroke and Research on a Novel Type of Decarboxylation Reaction. (2017)
Directed by Dr. Mitchell P. Croatt. 222 pp.

Isocarbacyclin is a valuable synthetic target that has been recognized as a potential neuroprotective agent against ischemic stroke. Herein we describe a step-economical synthesis of isocarbacyclin in an enantioselective fashion. The synthetic route utilizes a palladium-catalyzed decarboxylative coupling of a pentadienyl dienoate, a rhodium-catalyzed diene-diene [2+2+1] cycloaddition, and a ruthenium-catalyzed cross-metathesis reaction. The metathesis reaction is particularly valuable since it allows for late-stage diversification; as a result other analogues were synthesized from the same building block. Another new synthetic route will be described that was designed to use the same combination of metal-catalyzed reactions for the synthesis of a tricyclic isocarbacyclin analogue. Instead of completing the tricyclic analogue, a novel cyclization was discovered.

During the course of our synthesis of isocarbacyclin analogues, we discovered a decarboxylation reaction of a pentadienyl dienoate that did not require an anion stabilizing group. This novel decarboxylative coupling reaction, optimization, mechanistic evaluation, and substrate scope will also be described in detail.

SYNTHESIS AND BIOLOGICAL EVALUATION OF POTENT NEUROPROTECTIVE AGENTS AGAINST STROKE AND RESEARCH ON A NOVEL TYPE OF DECARBOXYLATION REACTION

by

Ghina'a I. Abu Deiab

A Dissertation Submitted to
the Faculty of The Graduate School at
The University of North Carolina at Greensboro
in Partial Fulfillment
of the Requirements for the Degree
Doctor of Philosophy

Greensboro
2017

Approved by

Dr. Mitchell P. Croatt
Committee Chair

APPROVAL PAGE

This dissertation written by GHINA'A I. ABU DEIAB has been approved by the following committee of the Faculty of The Graduate School at The University of North Carolina at Greensboro.

Committee Chair Dr. Mitchell Croatt

Committee Members Dr. Patricia Reggio

Dr. Nicholas Oberlies

Dr. Jason Reddick

December 14, 2016
Date of Acceptance by Committee

December 14, 2016
Date of Final Oral Examination

ACKNOWLEDGMENTS

Special mention goes to my advisor, Dr. Mitchell Croatt, for accepting me in his group and encouraging me to develop independent thinking and research skills. I have been extremely lucky and forever grateful to have an advisor who always helped and supported. I would like also to acknowledge my committee members Dr. Nicholas Oberlies, Dr. Patricia Reggio and Dr. Jason Reddick for their contributions to my dissertation.

Special acknowledgments for the department of Chemistry and Biochemistry at UNCG for the teaching assistantship and for Applied Sciences University in Jordan for the academic scholarship during the last year in my Ph.D. Program.

My thanks also goes to Dr. Kimberly Petersen and Dr. Nicholas Oberlies to allow me use their lab research facilities and to our collaborators, Dr. Rona Giffard at Stanford School of Medicine for the biological evaluation and Dr. Andrew Sargent and Dr. Andrew Morehead at East Carolina University for the decarboxylation computational study. All the thanks to the Croatt group members, especially to the authors of the decarboxylation paper, who have contributed immensely with my work in lab.

Last but not the least I would like to thank my family, my parents, sisters and brothers, for all the care and love that made my Ph.D. possible. And most of all to my husband who has instilled in me the confidence to achieve my dreams and the persistence to see every endeavor to completion. And finally to my triplets who added three more people waiting my success.

TABLE OF CONTENTS

Page

LIST OF TABLES

Page

LIST OF FIGURES

Page

LIST OF SCHEMES

Page

ABBREVIATIONS

Ac: acetate

APPI: Atmospheric Pressure Photoionization

Bz: benzoyl

calcd.: calculated

CH_2Cl_2: dichloromethane

CO: carbon monoxide

COSY: Correlation Spectroscopy

dba: dibenzylideneacetone

DBU: 1,8-Diazabicyclo[5.4.0]undec-7-ene

DCC: N,N'-Dicyclohexylcarbodiimide

DCE: 1,2-dichloroethane

DIBAL: Diisobutyl Hydride

DMAP: 4-dimethylaminopyridine

DME: dimethoxyethane

DMF: dimethylformamide

dppe: 1,2-bis(diphenylphosphino)ethane

eq: equivalents

et al.: and others

EtOAc: ethyl acetate

FDA: Food and Drug Administration

GC: gas chromatography

HCl: hydrochloric acid

HMBC: Heteronuclear Multiple Bond Coherence

HPLC: High Performance Liquid Chromatography

HRESIMS: High-resolution Electrospray Ionization Mass Spectrometry

hr: hours

HSQC: Heteronuclear Single Quantum Coherence

KHMDS: Potassium Hexamethyldisilazane

L: ligand

LiBr: lithium bromide

LiHMDS: Lithium Hexamethyldisilazane

LiOH: lithium hydroxide

M: molarity

MeOH: methanol

min: minutes

mL: milliliter

Ms: methane sulfonyl

NaH: sodium hydride

NaOH: sodium hydroxide

ng: nano gram

NMR: Nuclear Magnetic Resonance

NOESY: Nuclear Overhauser Effect Spectroscopy

ph: phenyl

ppm: part per million

rt: room temperature

TBS: *tert*-butyl dimethyl silyl

Temp: Temperature

Tf: trifluoromethyl sulfonyl

TFE: 2,2,2-trifluoroethanol

THF: tetrahydrofuran

μW: microwave

CHAPTER I

INTRODUCTION

1. Background and Significance

The last century has experienced development of synthetic strategies and syntheses of medicinal leads.[1] The total synthesis of synthetic or natural molecules exhibit almost infinite variations as they present puzzles that require scientists to solve challenges in their structures for which solutions are not available from known synthetic methods.[1] One of the challenges in total synthesis for many targets is the number of steps, which influences time, cost and amount of waste and byproducts.[2] It is for that reason, Wender *et al*. focus on the ***step economy*** in total synthesis to simplify complex therapeutic leads syntheses.[3–6] There are three approaches to achieve step-economical synthesis.[3,5,7] The first approach is to have a larger increase in target-relevant complexity per a step by developing new reactions. The second approach is based on targeting the function, not the structure, of medicinal agents and simplifying the target complexity which is a strategy of function-oriented synthesis.[3,6] The third approach is to achieve a late-stage diversification where subsequent analogues of the medicinal target could be synthesized from the same building block.

Isocarbacyclin (**1.2**), a synthetic analogue of prostacyclin, is one of the medicinal targets that was first synthesized in the 1980's (Figure 1.1).[8] Isocarbacyclin (**1.2**) has shown neuroprotective activity after ischemic stroke[9], however, studying its biological

activity was limited as a result of its syntheses with 15-20 steps by different research groups.[8,10–15]

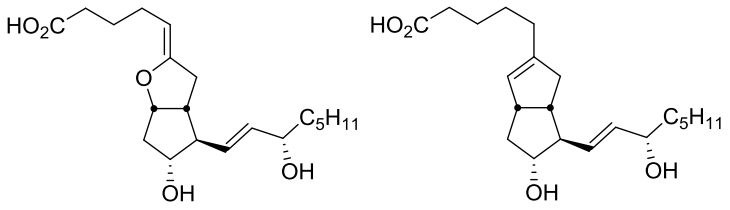
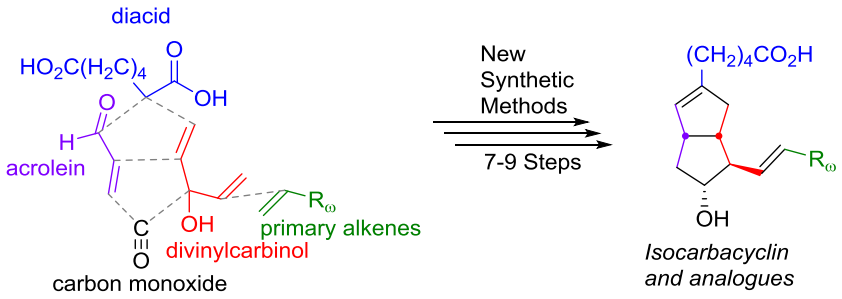


Figure 1.1. Prostacyclin (1.1) and Isocarbacyclin (1.2) Structures.

Herein, we present an enantioselective step-economical synthesis of isocarbacyclin (**1.2**) in only 9 steps utilizing inexpensive and commercially available starting materials (Scheme 1.1).[7,16] For this synthetic route we developed two new reactions: a decarboxylation of pentadienyl dienoate systems and [2+2+1] cycloaddition of bis-diene systems.[16]



Scheme 1.1. Step-Economical Synthesis of Isocarbacyclin and Its Bicyclic Analogues.

These two new reactions led to a rapid increase in the molecular complexity to afford the bicyclic core of isocarbacyclin (**1.2**) with four stereocenters as desired. Moreover a late-stage cross metathesis reaction enabled us to synthesize other analogues

of isocarbacyclin by using other simplified alkenes and from the same building block which further shorten the synthesis to 7 or 8 steps (Figure 1.2).

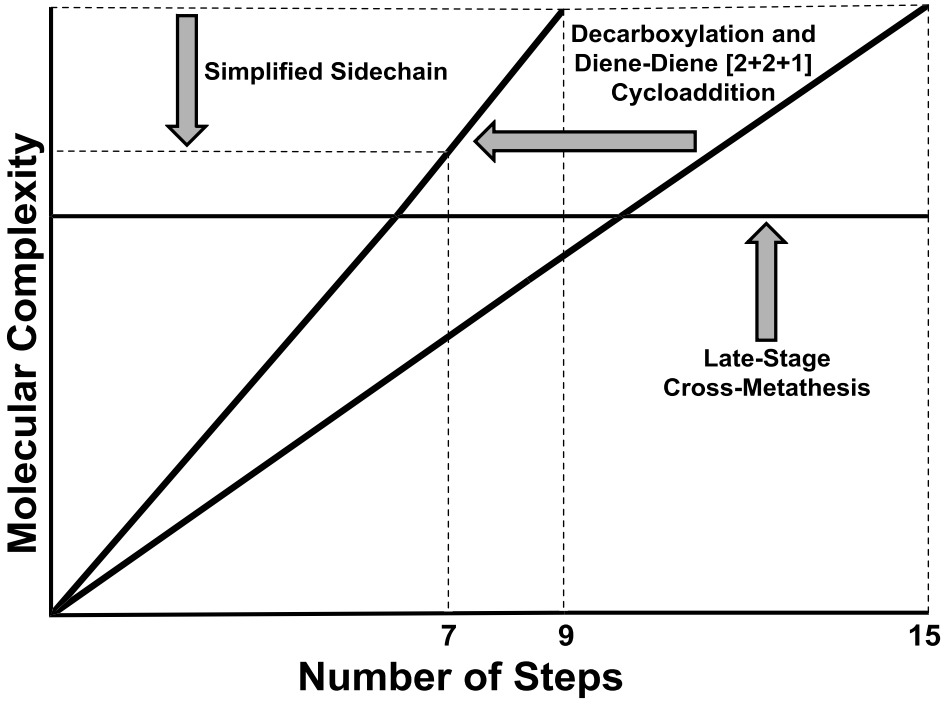
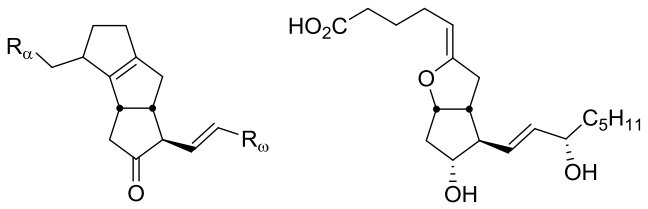


Figure 1.2. Utilization of Step-Saving Techniques in the Synthesis of Isocarbacyclin and Simplified Analogues.

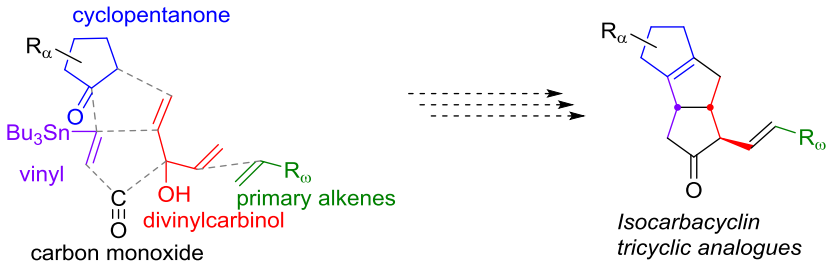
Despite the increase in the molecular complexity in the cycloaddition reaction, the yield for this step was low, which led us to develop a new synthetic route where we modified the starting bis-diene compound for the cycloaddition reaction. Moreover the structure of the final tricyclic analogue (**1.3**) was designed to position the α-side chain in a manner similar to prostacyclin (**1.1**, Figure 1.3).



tricyclic analogue, **1.3** Prostacyclin, **1.1**

Figure 1.3. Tricyclic Analogue (**1.4**) Structurally Is More Related to Prostacyclin (**1.1**).

A model system for the tricyclic analogues was prepared to test the two new reactions, decarboxylation and [2+2+1] cycloaddition. Having the novel reactions worked successfully a total synthesis was designed for the tricyclic analogues of isocarbacyclin. The total synthesis was designed in a way to use the same combination of the three metal-catalyzed reactions that were used previously in the synthesis of bicyclic analogues (Scheme 1.2).



Scheme 1.2. Step-Economical Synthesis of Tricyclic Isocarbacyclin Analogues.

The new decarboxylation reaction that was utilized for the synthesis of isocarbacyclin analogues is also described in greater detail. Metal-catalyzed cross-coupling reactions have had a great impact on the synthesis of biologically active synthetic and natural compounds.[17] Prominent among these reactions are the palladium-

catalyzed carbon-carbon bond-forming reactions.[17] One such reaction is decarboxylative coupling that utilizes a metal to generate organometallic intermediates that are coupled at the end (Figure 1.4).

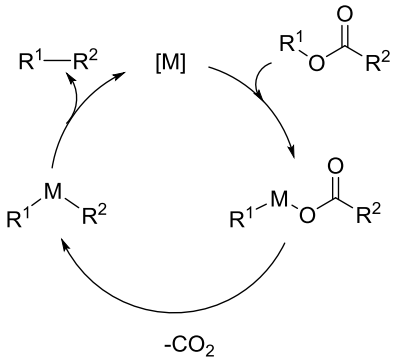
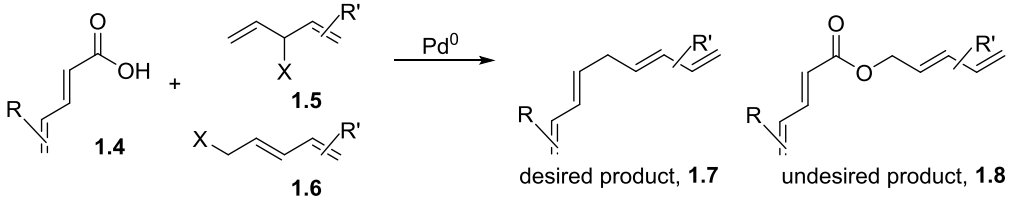


Figure 1.4. Decarboxylative Coupling.

A major limitation in the current decarboxylation reactions is that harsh conditions and an anion-stabilizing group are often required.[18–20] A decarboxylative coupling reaction was designed by Croatt research group of a dienoic acid (**1.4**) and bis-allylic (**1.5**) pentadienyl (**1.6**) substrates at ambient temperature without the need of anion-stabilizing group (Scheme 1.3). This reaction was also found to be successful for both intramolecular and intermolecular cases.



Scheme 1.3. Novel Decarboxylative Coupling of Dienoic Acids (**1.4**) and Bis-Allylic (**1.5**) or Pentadienyl (**1.6**) Substrates.

The novel decarboxylation was optimized for its catalyst, additives, solvent and temperature. Different reactions and conditions were screened to investigate the mechanism of this reaction with computational studies to propose two mechanisms. Having the conditions optimized, different substrates with substitutions on every unique position of both coupling substrates was examined. Substrates screened afforded either the desired product 1,3,6,8-tetraene (**1.7**) or the undesired rearranged ester (**1.8**, Scheme 1.3).

2. References

1. Nicolaou, K. C.; Montagnon, T. *Molecules that changed the world: a brief history of the art and science of synthesis and its impact on society*; Wiley-VCH: Weinheim, **2008**.

2. Newhouse, T.; Baran, P. S.; Hoffmann, R. W. *Chem. Soc. Rev.* **2009**, *38*, 3010–3021.

3. Wender, P. A.; Verma, V. A.; Paxton, T. J.; Pillow, T. H. *Acc. Chem. Res.* **2008**, *41*, 40–49.

4. Wender, P. A.; Croatt, M. P.; Witulski, B. *Tetrahedron* **2006**, *62*, 7505–7511.

5. Wender, P. A. *Nat. Prod. Rep.* **2014**, *31*, 433–440.

6. Wender, P. A.; Quiroz, R. V.; Stevens, M. C. *Acc. Chem. Res.* **2015**, *48*, 752–760.

7. Abu Deiab, G. I.; Croatt, M. P. In *Strategies and Tactics in Organic Synthesis*; Harmata, M., Ed.; Academic Press, **2017**; Vol. 12, pp. 95–117.

8. Sodeoka, M.; Ogawa, Y.; Mase, T.; Shibasaki, M. *Chem. Pharm. Bull. (Tokyo)* **1989**, *37*, 586–598.

9. Karasawa, Y.; Hitomi, T.; Komiyama, H.; Isobe, Y.; Kobayashi, T.; Yoshida, S.; Nakaike, S.; Araki, H. *Eur. J. Pharmacol.* **2002**, *449*, 127–133.

10. Sheddan, N. A.; Mulzer, J. *Org. Lett.* **2005**, *7*, 5115–5118.

11. Mase, T.; Sodeoka, M.; Shibasaki, M. *Tetrahedron Lett.* **1984**, *25*, 5087–5090.

12. Mandai, T.; Matsumoto, S.; Kohama, M.; Kawada, M.; Tsuji, J.; Saito, S.; Moriwake, T. *J. Org. Chem.* **1990**, *55*, 5671–5673.

13. Hashimoto, S.; Shinoda, T.; Ikegami, S. *J. Chem. Soc. Chem. Commun.* **1988**, 1137–1139.

14. Hashimoto, S.; Shinoda, T.; Shimada, Y.; Honda, T.; Ikegami, S. *Tetrahedron Lett.* **1987**, *28*, 637–640.

15. Kramp, G. J.; Kim, M.; Gais, H.-J.; Vermeeren, C. *J. Am. Chem. Soc.* **2005**, *127*, 17910–17920.

16. Nagy, E. E.; Hyatt, I. F. D.; Gettys, K. E.; Yeazell, S. T.; Frempong, S. K.; Croatt, M. P. *Org. Lett.* **2013**, *15*, 586–589.

17. Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem. Int. Ed.* **2005**, *44*, 4442–4489.

18. Jana, R.; Partridge, J. J.; Tunge, J. A. *Angew. Chem. Int. Ed. Engl.* **2011**, *50*, 5157–5161.

19. Waetzig, S. R.; Tunge, J. A. *J. Am. Chem. Soc.* **2007**, *129*, 14860–14861.

20. Lang, S. B.; O'Nele, K. M.; Tunge, J. A. *J. Am. Chem. Soc.* **2014**, *136*, 13606–13609.

CHAPTER II

STEP-ECONOMICAL SYNTHESIS OF CLINPROST AND ANALOGUES UTILIZING A NOVEL DECARBOXYLATION REACTION

Abu Deiab, G. I.; Croatt, M. P. In *Strategies and Tactics in Organic Synthesis*; Harmata, M., Ed.; Academic Press, **2017**; Vol. 12, pp. 95-117.

Chapter Outline

Abstract: We present our step-economical synthesis of clinprost, the methyl ester of isocarbacyclin, and analogues. Isocarbacyclin is a valuable target due to its neuroprotection from the oxidative damage after a stroke. Specifically, we utilized a palladium-catalyzed decarboxylative coupling of a pentadienyl dienoate, a rhodium-catalyzed diene-diene [2+2+1] cycloaddition, and a ruthenium-catalyzed cross-metathesis reaction. The decarboxylation reaction is the first decarboxylation of its type since the carboxyl-bearing carbon does not possess an anion-stabilizing group. In this chapter, we present some of our research into this novel reaction. The diene-diene [2+2+1] cycloaddition is the first cyclocarbonylation between two dienes. The metathesis reaction is particularly valuable since it allows for late-stage diversification. These three metal-catalyzed reactions enabled us to complete the synthesis of clinprost in nine steps, seven for some analogues, instead of the 15 or more steps that have been previously reported.

Keywords: Isocarbacyclin, clinprost, stroke, neuroprotection, step-economy, new reactions, decarboxylation, diene, pentadienyl dienoate, bicycle, metathesis, cycloaddition, palladium, rhodium, ruthenium

1. Introduction and Background

1.1 Step Economy in Organic Synthesis

During the early stages of synthetic organic chemistry, the major efforts were to determine if the synthesis of certain compounds was ***possible***. There were many incredible accomplishments[1] including the syntheses of morphine,[2] strychnine,[3,4] quinine[5,6] and taxol.[7–12] While continuing research efforts in this first area, later research

added in the aspect of learning to make compounds more ***selectively***. Efforts with regioselectivity, diastereoselectivity, and enantioselectivity were all studied and resulted in many tremendous discoveries including reactions dealing with the Diels-Alder cycloaddition,[13] the aldol reaction,[14] and various oxidations[15] and reductions.[16] In more recent years, research has centered on making compounds in a more ***practical manner***. With this last focus, significant efforts have focused on items relating to step,[17] atom,[18] and redox[19,20] economies. All of these economies tie in with efforts to approach the ideal synthesis, which is a synthesis that occurs in one step from readily available starting materials and in 100% yield, and includes facile product isolation and no waste generation.[21]

In order to approach the ideal synthesis, efforts in our group have focused primarily on the step economy aspect. This is because the number of steps of a synthesis has a strong correlation with many of the important aspects of the ideal synthesis. There are essentially three ways to shorten the number of steps of a synthesis, which relates to the molecular complexity of the target (Figure 2.1, top graph). These options are to have a steeper slope for the complexity increase per step (left graph), decrease the complexity of the target (center graph), or use a more complex starting material (right graph). Importantly, all three of these approaches can be used together to synergistically shorten the number of steps in a synthesis (bottom graph).

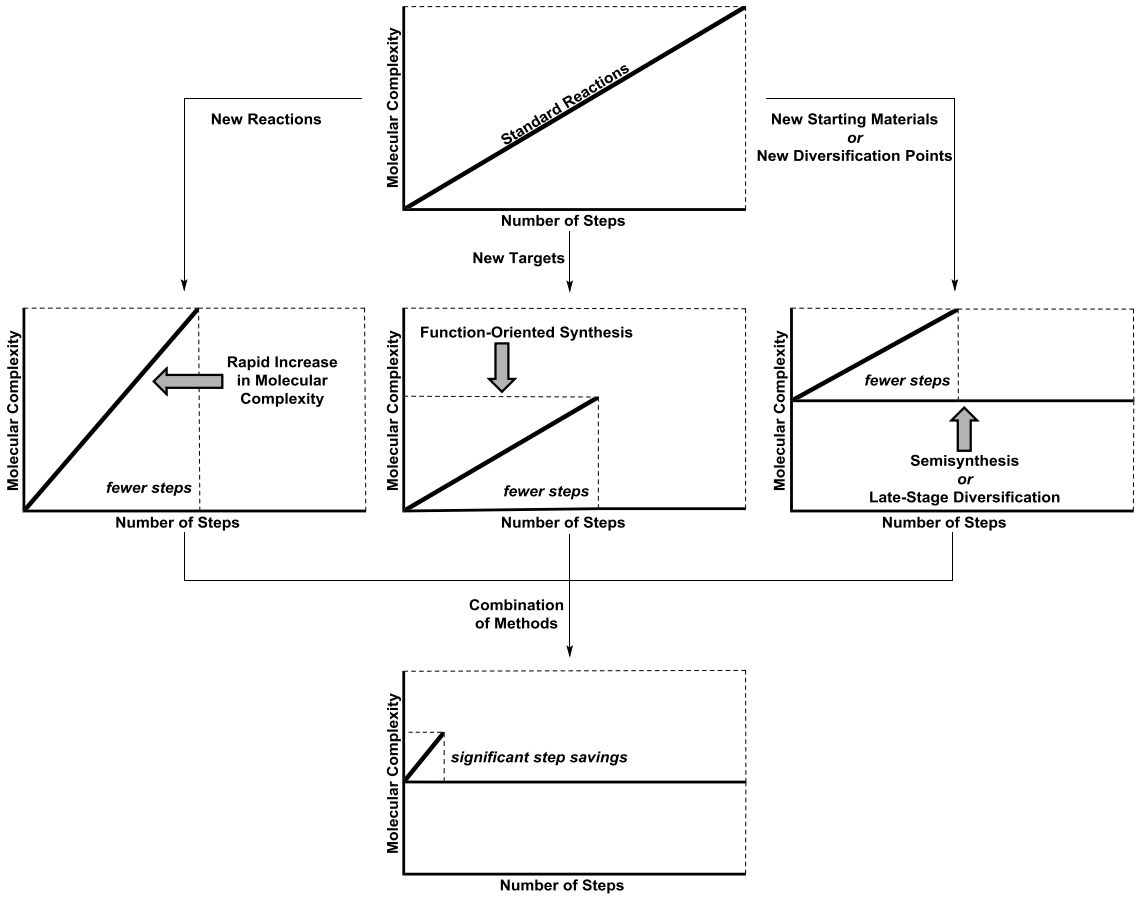


Figure 2.1. Strategies to Improve Step Economy in Organic Synthesis.

The left graph of Figure 2.1 requires the design and development of new reactions that have a more rapid increase in target-relevant molecular complexity.[22] Two examples of this approach being used in synthesis are Reppe and Toepel's synthesis of cyclooctatetraene[23] and Wender's synthesis of silphinene.[24] The first synthesis of cyclooctatetraene by Willstätter and Wasser was highly significant, however, it required 13 steps from a complex starting material with a 2% overall yield.[25] Twenty-nine years later Reppe and Toepel were able to perform a cyclotetramerization of acetylene to

generate large quantities of cyclooctatetraene.[23] Wender's synthesis of silphinene utilized an arene-alkene meta-photocycloaddition to introduce significant target-relevant molecular complexity and synthesize the target in only three steps from simple starting materials instead of 10-21 steps, as has been reported by others.[22,26]

The center graph (Figure 2.1) appears to be overly simplifying the process since it is changing the target complexity, but this is a strategy of function-oriented synthesis.[10] Instead of only targeting a structure, the goal is to target the function of a structure and simplify it while retaining or improving on the function. This is what often occurs in pharmaceutical companies when modifying a complex natural product to develop an active pharmaceutical ingredient. A recent example is the development of fingolimod as a drug for multiple sclerosis by chemical modification of a natural product myriocin.[27,28] Myriocin was isolated from a fungus and had three stereocenters and would have been moderately difficult to synthesize. Optimization of the structure decreased the complexity and removed all stereocenters to obtain a more easily synthesized structure while maintaining activity.

The right graph (Figure 2.1) can represent two different opportunities to synthesize compounds. First, this could represent semisynthesis, which is how Taxol® is currently being produced.[29] Taxol® and its derivatives were not only game-changers for the treatment of cancer but have been, and continue to be, blockbuster drugs.[30] *De novo* synthesis of Taxol® was not practical to access sufficient quantities,[7–12] but a related structure, 10-deacetylbaccatin III, can be used to start with more molecular complexity.[7] The other approach that is represented by the right graph is late-stage diversification.

Although late-stage diversification does not increase the molecular complexity of the starting material, it accesses an intermediate with higher complexity. Thus, subsequent analogues do not need to start from the complexity of the starting material but from the complexity of the branching point. This decreases the total number of steps for the synthesis of analogues.

The bottom graph represents what happens when all three of these step-shortening techniques are used together. As illustrated by that graph, there can be even more significant step-savings when two or more approaches are used. In the synthetic route presented in this chapter, all three approaches were combined through the use of new reactions. This led to a rapid increase the molecular complexity, a function-oriented synthesis to decrease the molecular complexity of the target, and a late-stage diversification to decrease the total number of steps for analogues.

1.2 Prostacyclin and Its Activity

Prostacyclin (**2.1**), an endogenous bicyclic prostaglandin (PGI_2), was structurally characterized in 1976 by the research group of John Vane, a biochemist in the United Kingdom (Figure 2.2).[31] It is biologically synthesized from arachidonic acid and commonly prescribed under the name of Flolan® (epoprostenol) for patients with primary pulmonary hypertension.[32,33] Prostacyclin (**2.1**) is a highly potent vasodilator and inhibitor of platelet aggregation; however, it is unstable due to the labile nature of the vinyl ether in the bicyclic ring system.[31,34] Having a half-life of minutes *in vitro*, prostacyclin use in clinical applications is limited. This fact led to the development of

new analogues with the aim of generating chemical stability while maintaining or improving the physiological activity.[35] The first generation of analogues simply replaced the ethereal oxygen with a methylene group with no other changes in structure.[36] This analogue, known as carbacyclin (**2.2**; Figure 2.2), was indeed more stable, but showed significant side effects, such as headache and severe facial flushing during clinical trials.[37]

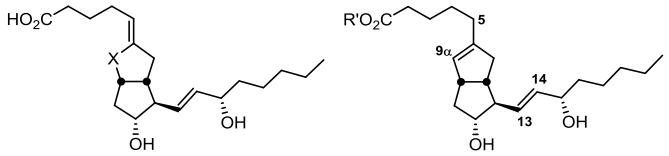


Figure 2.2. Prostacyclin and its Analogues.

The second generation of synthetic analogues isomerized an alkene, which led to the development of clinprost (**2.3**; Figure 2.2) and its active metabolite isocarbacyclin (**2.4**), both of which were found to be more stable than prostacyclin (**2.1**).[38–41] In addition to vasodilation, isocarbacyclin and its methyl ester, clinprost, were found to have neuroprotective activity in animal models following ischemic stroke. Isocarbacyclin possesses a bicyclo[3.3.0]octene system with four stereocenters and a sidechain connected to the exocyclic alkene, which is called the ω-sidechain, and another α-sidechain that contains the carboxylic acid moiety. The R_α and R_ω nomenclature derives from the α and ω parts of arachidonic acid, which is the biosynthetic precursor for prostacyclin (**2.1**).

Importantly, the only treatment currently approved for ischemic stroke includes anticoagulant medicines like warfarin and antiplatelet medicines like aspirin and Plavix® (clopidogrel).[42] These are only effective in treating vasoconstriction and blood clot dissolution by restoring blood flow to the affected area of the brain and preventing recurrent ischemic stroke for patients. Thus, the need for additional potential treatments that protect against neuronal damage in the brain following ischemic attack is urgent and increasing. As research continued, the third generation of isocarbacyclin analogues (Figure 2.3) was reported in 1996, including 15*S*-TIC (**2.5**; 15*S*-16-*m*-tolyl-17,18,19,20-tetranorisocarbacyclin), 15*R*-TIC (**2.6**) and 15-*deoxy* TIC (**2.7**).[43,44] These analogues were synthesized to test the necessity of the alcohol functional group in the ω-sidechain as well as the role of stereochemistry in that position. It was found that removing the alcohol functionality or reversing its stereochemical configuration completely diminished the vasodilation effect and only protection against neuronal death remained.[45]

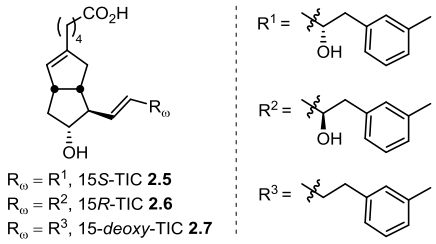


Figure 2.3. Isocarbacyclin Analogues for Testing the Necessity of the Alcohol Functional Group.

As previously stated, the vasodilating capabilities of prostacyclin (**2.1**) have been known for decades and it was shown to be helpful for patients with pulmonary

hypertension. It was also hypothesized to be helpful to patients with ischemic stroke.[46] There are two types of stroke, hemorrhagic and ischemic. Hemorrhagic strokes occur when blood vessels in the brain are weak and burst to cause bleeding. Ischemic strokes, which accounts for about 87% of reported strokes,[47] are caused by blood clots in the brain that lead to reduced blood flow and, as a result, reduced availability of oxygen and glucose in the affected area.[48] This reduction in blood flow is followed by rapid influx of reactive oxygen species, a process known as reperfusion, after circulation of blood is restored. Both the initial low oxygen and glucose levels and the subsequent reperfusion cause extensive damage to the neurons.[49] Isocarbacyclin (**2.4**) and its analogues were found to show a protective effect against neuronal damage following ischemic stroke in animal models.[38–41] Different synthetic methods for isocarbacyclin and its analogues have been reported by several groups; however, most are more than 20 steps with the shortest being 15 steps from commercially available starting materials.[43,44,50–55] Synthetic challenges, including the construction of the bicyclic ring system, regioselectivity of both the endocyclic double bond (C6-C9α), and the α-sidechain, are some of the reasons for the long syntheses.[43,44] Moreover, there is the problem of how to selectively introduce the four stereocenters and the variability in regard to the ω-sidechain. The total synthesis of isocarbacyclin methyl ester, clinprost (**2.3**), was published by our research group in 2013.[56] Three late-stage steps in the synthesis use different transition metal-catalyzed reactions to rapidly assemble the target. The introduction of complexity and chemoselectivity resulted in an enantioselective synthesis of clinprost (**2.3**) that is nine total steps from commercially available starting materials.

In most of the prior syntheses, optically active starting materials were used to synthesize isocarbacyclin (**2.4**) and different analogues.[43,44,50–55] Many of these synthetic routes involve either annulation of a five-membered ring onto an optically active cyclopentane derivative (**2.8** – **2.11**; Figure 2.4) that is commercially available or using a staring material that already has a bicyclo[3.3.0]octane skeleton (**2.12** and **2.13**; Figure 2.4). An issue that limited these approaches is how to selectively introduce the endocyclic double bond.

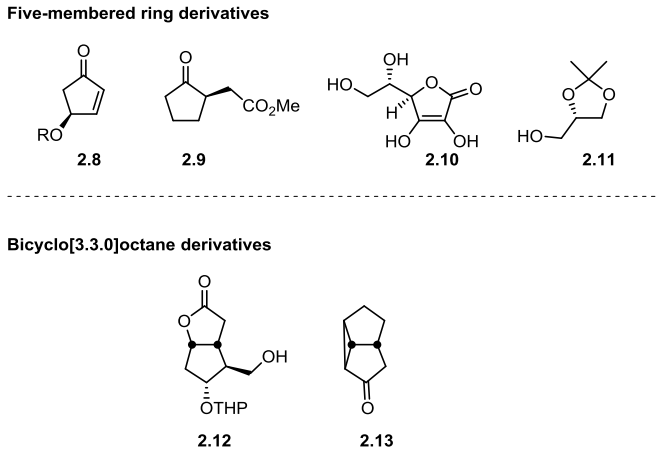


Figure 2.4. Optically Active Starting Materials Used Previously for Different Isocarbacyclin Syntheses.

In 2005, Neil Sheddan and Johann Mulzer reported a new route for the synthesis of 15*S*-TIC (**2.5**), 15*R*-TIC (**2.6**) and 15-*deoxy* TIC (**2.7**) that takes advantage of two key reactions: the regioselective generation of the endocyclic double bond with an sp^2-sp^3 palladium-catalyzed cross-coupling reaction (C5-C6) to install the α-sidechain and the generation of the exocyclic double bond by Julia-Kocienski olefination to install the ω-

sidechain at a late stage in the synthesis (Figure 2.5).[57] However, this approach still required 20 steps. One year later the same group reported another synthesis for the same analogues in which the ω-sidechain was installed by a cross metathesis reaction (Figure 2.5).[58] While this approach allows for diversity of R_ω, the synthesis still needed four subsequent steps to access each analogue after the metathesis reaction.

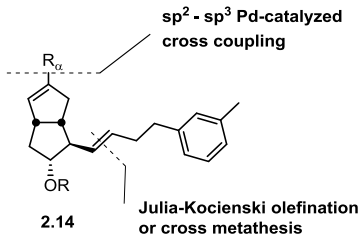


Figure 2.5. Sheddan and Mulzer's Synthetic Approaches to Isocarbacyclin Analogues.

2. Retrosynthetic Analysis

The synthetic routes that have been reported for isocarbacyclin (**2.4**) and its analogues require at least 15 steps and most allow for very little diversification of the key ω-sidechain. While examining the functionality produced by a rhodium-catalyzed diene-ene [2+2+1] cycloaddition, which has been previously reported by Mitchell Croatt and Paul Wender[58] (Figure 2.6), it was noted that alkenyl cyclopentanone core system **2.16** resulting from this reaction is similar to the isocarbacyclin bicyclic core system. This cycloaddition involves a diene-ene reactant, which, when treated with 10 mol % of a rhodium(I) catalyst under carbon monoxide atmosphere, smoothly converts to the [2+2+1] product with the formation of three stereocenters that have the same relative stereochemical configuration as the isocarbacyclin bicyclic core. It was envisioned that

reduction of the ketone would selectively occur from the convex face of the bicycle to generate the correct carbinol stereochemistry.

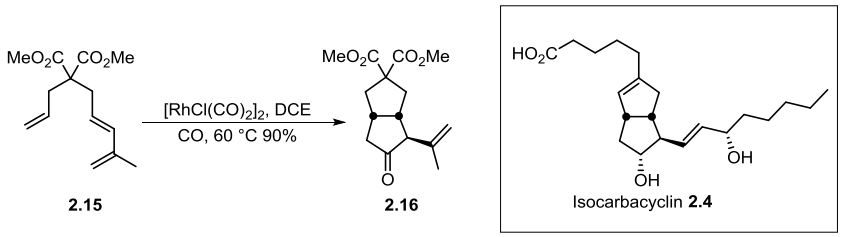


Figure 2.6. Diene-ene [2+2+1] Cycloaddition and Comparison with Isocarbacyclin.

Based on the 2006 report by Sheddan and Mulzer using cross metathesis to synthesize isocarbacyclin analogues (Figure 2.7), it was envisioned that the remaining olefin from the [2+2+1] cycloaddition could be attached to the R_ω sidechain.[57] Furthermore, different alkenes could be installed to get different ω-sidechains from a single compound at a late-stage in the synthesis. Due to the availability of alkenes and the target-relevant complexity of the bicyclic core, this approach could have a high level of step economy.

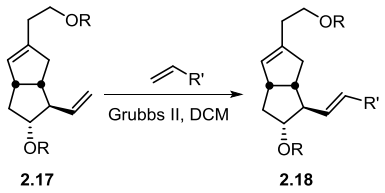
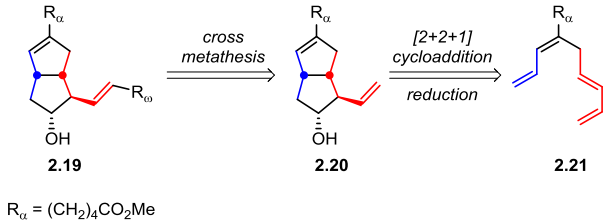


Figure 2.7. Cross Metathesis for the Synthesis of Isocarbacyclin Analogues.

With these results in mind, we were attracted to two key points. The first was that building the complex bicyclic core system (**2.20**), with the four stereocenters as desired,

could be achieved by diene-ene [2+2+1] cycloaddition of bis-diene (**2.21**) followed by reduction. The second attractive point was the diversification that could be achieved by cross metathesis at a late stage to get different analogues from the same bicyclic core (**2.20**). As a result, a retrosynthesis was conceived (Scheme 2.1) of isocarbacyclin methyl ester, or clinprost (**2.3**), having only nine steps.[56] The first part of the synthesis, and most difficult part, was to generate bis-diene (**2.21**).

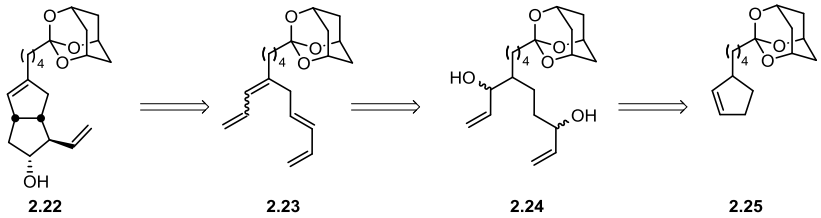


Scheme 2.1. Retrosynthesis for Clinprost and Analogues

3. Synthesis of the Bis-Diene Building Block

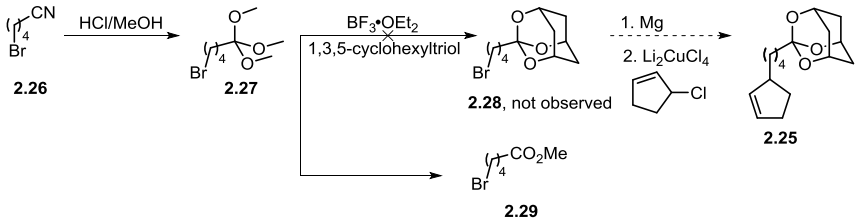
3.1 Ortho-ester Approaches

Our first generation attempt to synthesize isocarbacyclin analogues utilized ortho esters with the R_α-sidechain so that simple hydrolysis would generate the final analogues after assembling the bicyclic core (**2.22**; Scheme 2.2). It was envisioned that the bis-diene (**2.23**) could be formed by double dehydration of diol **2.24**. Diol **2.24** could be formed by a reaction of two vinyl-Griniard reagents with a dialdehyde resulting from ozonolysis of cyclopentene **2.25**.



Scheme 2.2. Retrosynthesis of Ortho Ester **2.22**.

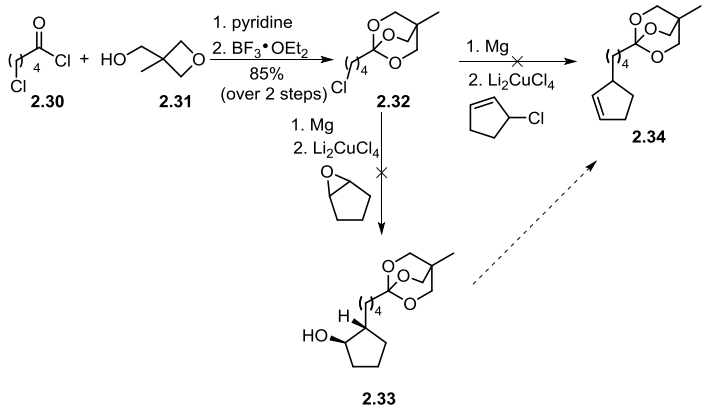
The first ortho ester was derived from cyclohexanetriol (Scheme 2.3). The conversion of nitrile **2.26** to the cyclohexyl ortho ester (**2.28**) first traversed trimethyl ortho-ester **2.27**.[59] After multiple attempts to form and utilize cyclohexyl ortho ester **2.28**, it was determined that hydrolysis to the ester (**2.29**) was sufficiently problematic. Hydrolysis could be dealt with if needed, but instead it was decided to use an alternative ortho ester protecting group.



Scheme 2.3. Preparation of Ortho Ester from Cyclohexanetriol.

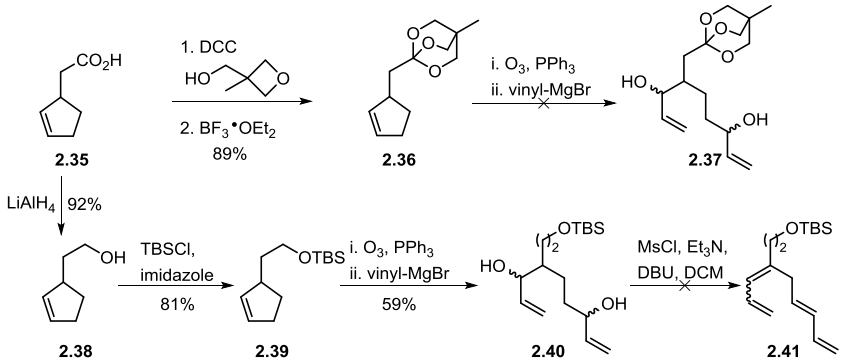
The second ortho ester examined was derived from oxetane **2.31** (Scheme 2.4). Formation of this ortho ester (**2.32**) proceeded much better and it was much more stable.[60] Unfortunately, attempts at subsequent coupling reactions, by formation of the cuprate, were not successful with either cyclopentenyl chloride or cyclopentene oxide. Although both of these electrophiles are highly reactive, alternative intramolecular

reactions were possible, in addition to hydrolysis of the ortho ester or decomposition of the electrophiles.



Scheme 2.4. Attempted Application of Ortho Ester **2.32**.

At this stage in the project, we decided to use a model system to try and learn more about the potential of future steps in the synthetic route. As such, the ortho ester of acid **2.35** was formed (**2.36**; Scheme 2.5). Ozonolysis and addition of vinyl Grignard was not successful; however, the failure of this process was possibly due to cleavage and decomposition of the ortho ester. To further simplify the process, the acid was protected by reduction to the alcohol (**2.38**) and formation of the silyl ether **2.39**. While this was not ideal for an eventual synthetic route for reasons of step/atom/redox economy,[17–20] a silyl ether would be more stable to future conditions and help determine the feasibility of the route. In this case, the result was that a one-flask ozonolysis and Grignard reaction was possible, with an adequate yield of diol **2.40** (59%).

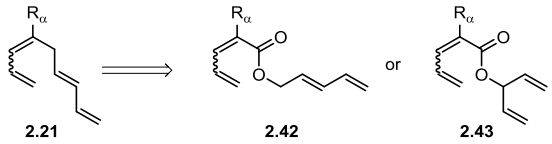


Scheme 2.5. Synthesis of Diol **2.40**.

With diol **2.40** in hand, only a double dehydration was required to form the desired tetraene **2.41**. Although simplistic on paper, this reaction is complicated by a number of features. First, after one of the hydroxy groups was converted into a leaving group, the remaining alcohol rapidly cyclized to form a cyclic ether. Another issue was that the targeted tetraene was going to be especially prone to isomerization to the fully conjugated system or oligomerization/polymerization due to the high percentage of conjugated alkenes present. Therefore, strongly acidic or basic conditions were considered to be incompatible with the tetraene, but mild acids or bases would be required for elimination. Unfortunately, all of the conditions attempted for the double elimination, including Appel conditions[61] and MsCl, led to only cyclization, polymerization, or other routes of decomposition. The conclusion that was gleaned from these failed approaches was that the synthesis of the bis-diene was not as simple as initially considered and that more neutral conditions would be required for its generation. To solve this problem, we decided to move into the area of organometallics.

3.2 Decarboxylation Approach

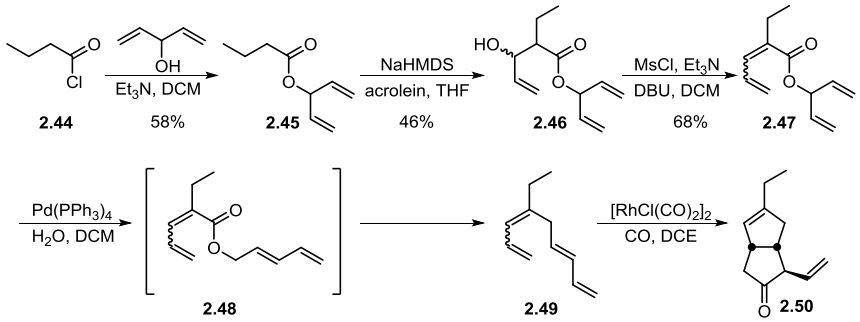
While considering the many metal-catalyzed options to generate the bis-diene, the opportunity to utilize a palladium(0)-catalyzed allylic decarboxylation appeared especially attractive (Scheme 2.6). Metal-catalyzed allylic substitutions and decarboxylative couplings have been examined and have been the topics of reviews.[62,63] For the system that fits for the requisite bis-diene (**2.21**), the ideal decarboxylation precursor would be a linear (**2.42**) or a branched (**2.43**) pentadienyl dienoate. Although there are numerous reports of allylic substitutions, there were only very limited reports of pentadienylic substitutions,[64] and no reports of decarboxylative couplings with a dienoate. These facts resulted in this route having a higher level of risk. However, since previous routes were unsuccessful, and necessity is the mother of invention, we felt that this process was worth exploring.



Scheme 2.6. Retrosynthesis of **2.21**.

Before dedicating efforts to the synthesis of the specific system required, a model system was again utilized (Scheme 2.7). As such, butyryl chloride was reacted with divinyl carbinol, the resulting ester (**2.45**) was deprotonated and reacted with acrolein, and elimination via the mesylate yielded pentadienyl dienoate **2.47** as a mixture of *E* and *Z* isomers. Gratifyingly, after subjecting ester **2.47** to $Pd(PPh_3)_4$ in dichloromethane at 50

°C, significant amounts of decarboxylated product were formed. This was not only the first Pd-catalyzed allylic decarboxylative coupling of a system of this type, but also a major breakthrough in this project since we finally synthesized the bis-diene. This decarboxylative coupling is unique for several reasons, including requiring an equivalent of water for success. This will be discussed in greater detail in Section 5. Although the resultant tetraene **2.49** was relatively volatile ($C_{11}H_{16}$), it could be characterized and was used to test the viability of the next Rh(I)-catalyzed cycloaddition reaction. A definitive yield wasn't obtained for reasons of scale and volatility; however, it was clear that the cycloaddition was successful. Given the success of these two key reactions, we decided to generate the structures required for the actual system.



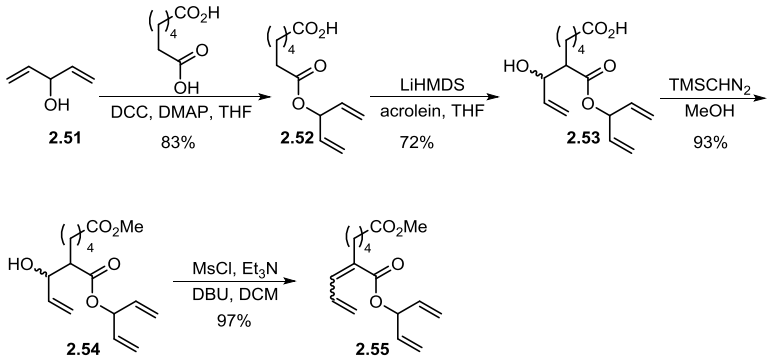
Scheme 2.7. Model Study for Tetraene Formation.

4. Synthesis of Clinprost and Analogues

4.1 Synthesis of the Bicyclic Core

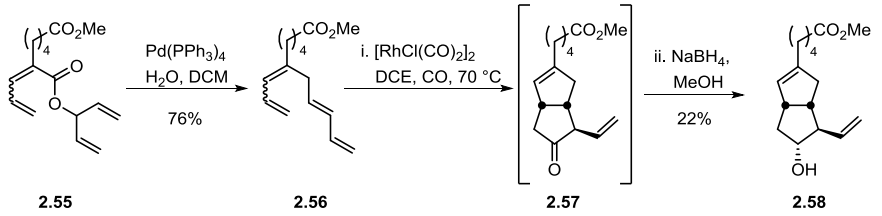
Our synthetic plan (Scheme 2.8) initiated with the preparation of the key bis-diene building block of clinprost (**2.3**) from commercially available, inexpensive starting materials. As such monoesterification of pimelic acid with divinyl carbinol easily

accessed ester **2.52** using DCC and DMAP. The use of excess pimelic acid allowed for scalability, efficiency and separability using the insolubility of pimelic acid and dicyclohexyl urea in hexane. This esterification was followed by aldol condensation with acrolein at the alpha position of the ester using 3 equivalents of solid LiHMDS. The resulting compound (**2.53**) was converted to its methyl ester (**2.54**) using diazomethane and finally dehydration via the mesylate with DBU afforded pentadienyl dienoate **2.55**.



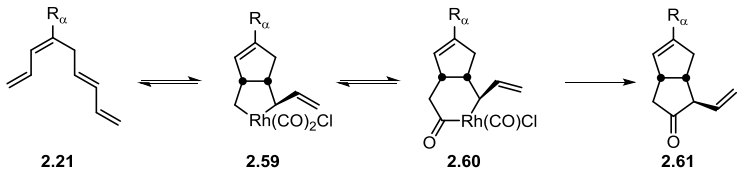
Scheme 2.8. Synthesis of Tetraene Precursor **2.55**.

Ester **2.55** was then subjected to a Pd(0)-catalyst which resulted in a simultaneous decarboxylation of the allyl ester and allylic rearrangement to form the building block of this synthesis (**2.56**; Scheme 2.9). It was determined that bis-diene **2.56** was relatively stable when pure, but trace impurities sometimes led to rapid polymerization. For this reason, bis-diene **2.56** was typically used in subsequent reactions within one week. Bis-diene **2.56** was reacted with 10 mol % of a rhodium (I) catalyst under carbon monoxide atmosphere, followed by reduction using sodium borohydride, to yield the completed bicyclic core (**2.58**).



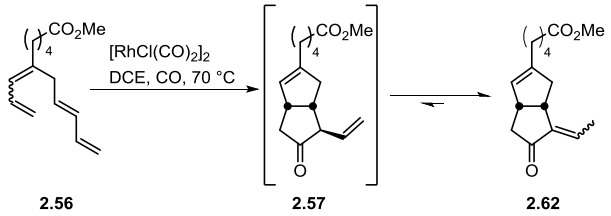
Scheme 2.9. Synthesis of the Clinprost Core.

There is a major increase in the molecular complexity for this [2+2+1] cycloaddition reaction during which both rings are assembled and four stereocenters are set with the required relative stereochemistry after *in situ* reduction from the convex face of the bicycle using sodium borohydride (Scheme 2.9). The mechanism through which this [2+2+1] reaction proceeds has been previously studied (Scheme 2.10).[65] When the rhodium catalyst comes into contact with the olefins, it undergoes an oxidative cyclization and forms the first ring of the bicycle as seen in intermediate **2.59**. The rhodium then inserts one of its carbonyl ligands into the rhodacycle **2.59**, thereby expanding it by one carbon (**2.60**). Finally, reductive elimination occurs and the reduced rhodium species is released from intermediate (**2.60**). The carbon monoxide atmosphere under which the reaction is kept allows coordination of another carbonyl ligand and the rhodium catalyst is then ready to reenter the catalytic cycle. The [2+2+1] cycloaddition of diene-enes,[65] diene-ynes[66] and diene-allenes[67] has been reported, however, our synthesis of clinprost is the first report of a diene-diene [2+2+1] cycloaddition.



Scheme 2.10. Rhodium-Catalyzed Diene-Diene [2+2+1] Cycloaddition.

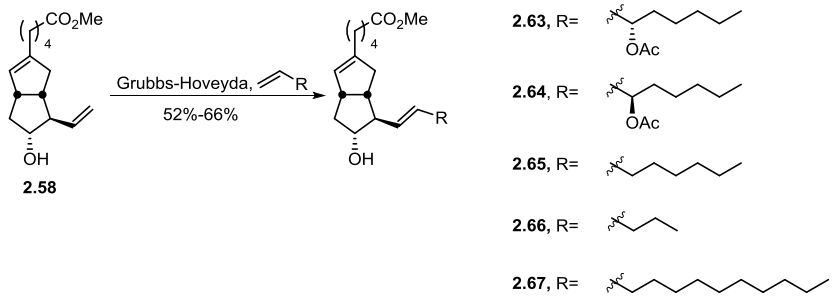
The yield for the diene-diene [2+2+1] reaction is low in part because only the *Z*-isomer of bis-diene **2.56** reacts to give bicyclic ketone **2.57** while the *E*-isomer remains unreacted. Moreover, ketone **2.57**, formed after the cycloaddition, isomerizes quickly to the more stable and undesired α,β-unsaturated ketone isomer (**2.62**; Scheme 2.11). Different conditions were examined in order to maximize the yield of the [2+2+1] carbonylative cycloaddition. The reaction could be performed in triflouroethanol (TFE), despite the quick isomerization of the desired product, but dichloroethane (DCE) worked most efficiently for this reaction. Running the reaction for longer than 9 hours at 80 °C increased the isomerization to the undesired enone (**2.62**). Different temperatures were screened only to obtain completely or mostly the undesired product. The loading of the rhodium catalyst was increased to more than 10 mol % without showing an effect on the yield. An additive, silver hexaflouroantimonate, was also tried, but mainly the isomerized undesired product resulted. It was found that running this reaction at 70 °C in DCE for 8 hours gives the highest yield at 22%.



Scheme 2.11. Isomerization of the Bicyclic Ketone.

4.2 Synthesis of Clinprost and Analogues from the Bicyclic Core

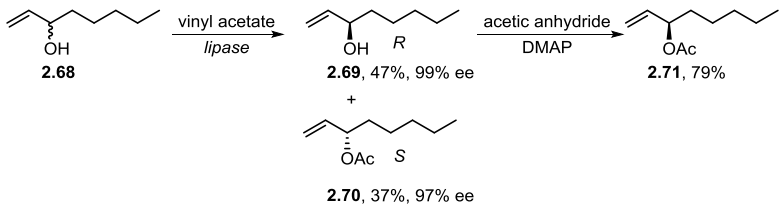
With the bicyclic core (**2.58**) in hand, different compounds could be synthesized from the same penultimate intermediate, allowing for late-stage diversification. Different ω-sidechains were installed via ruthenium(II)-catalyzed cross metathesis using different alkenes (Scheme 2.12). Since this type of reaction was previously reported in a very similar structure by Sheddan and Mulzer,[57] we were confident that the reactions would be successful.



Scheme 2.12. Introduction of ω-sidechains via Cross Metathesis.

The alkenes used were either commercially available (**2.65** – **2.67**) or could be accessed by one or two steps (**2.63** and **2.64**; Scheme 2.13). As shown, using enzymatic resolution of racemic 1-octen-3-ol (**2.68**),[68] we were able to synthesize alkenes **2.69** and

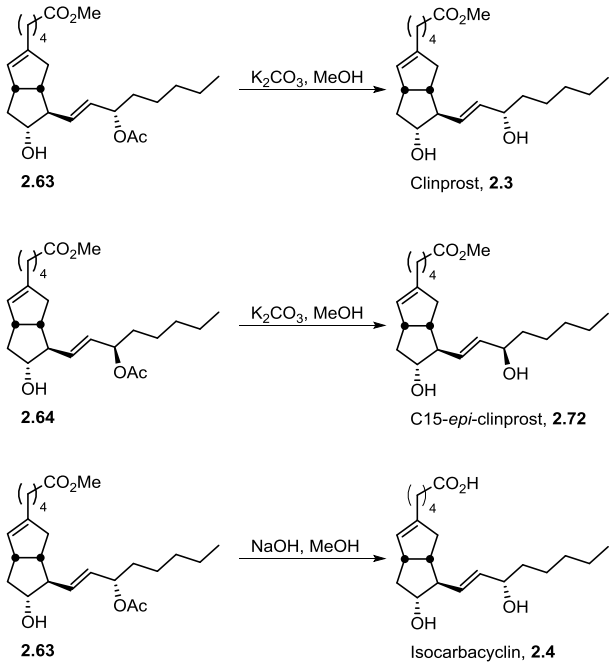
2.70 with high enantioselectivity. When alkenes **2.69** or **2.70** were reacted with bicyclic core **2.58**, two diastereomers were produced that were separated by column chromatography to get protected analogues **2.63** and **2.64** with high enantiopurities.



Scheme 2.13. Resolution of Allylic Alcohol **2.68**.

Hydrolysis of the acetate group in compounds **2.63** and **2.64** (Scheme 2.14) gave the two analogues, clinprost (**2.3**) and its C15-epimer (**2.72**) in nine total steps. The deoxy analogues (**2.65** - **2.67**) required only seven total steps, which is less than half as many as previously reported analogues. Clinprost, its epimer, deoxyclinprost (**2.65**) and the bicyclic core (**2.58**) were tested for their neuroprotective ability in the lab of Dr. Rona Giffard at Stanford Medical School. The Giffard lab tests neuroprotection by a model of ischemia using cortical neurons isolated from embryonic mouse brains. They use primary cultures to more closely approximate normal neurons using assays that mimic ischemic conditions. The compounds that were synthesized were found to be less active than isocarbacyclin (**2.4**), the free acid of clinprost. Specifically, clinprost was neuroprotective at 5 μM concentration, but only when the injury to the nerve cells was reduced to moderate levels. This indicates that free acid is required for activity. Isocarbacyclin (**2.4**),

the free acid of clinprost, and other analogues with the free acid moiety could be obtained by hydrolysis of the ester. Hydrolysis was previously reported using NaOH in methanol (Scheme 2.12).[52]

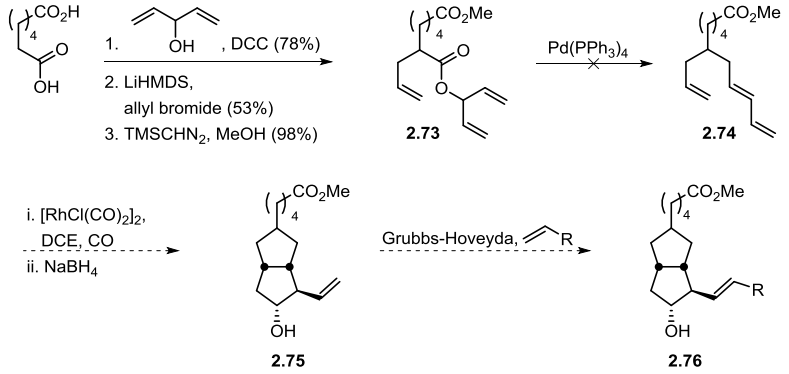


Scheme 2.14. Ester Hydrolysis of Clinprost Analogues.

4.3 Efforts for the Synthesis of Saturated Bicyclic Analogues

It was thought that a new type of analogue that does not contain the endocyclic double bond could be synthesized in almost exactly the same manner. Instead of the mono-esterified pimelic acid undergoing the aldol reaction with acrolein, an allyl group could be installed via a simple enolate alkylation reaction. Subsequent methylation, elimination, decarboxylation, cycloaddition, and cross-metathesis steps could be performed in the same manner as before with the result being a more saturated analogue

(**2.76**; Scheme 2.15). The synthesis to generate diester **2.73** proceeded as planned, however, numerous decarboxylation conditions failed.



Scheme 2.15. Proposed Synthesis of Ring-Saturated Analogues of Clinprost.

As mentioned earlier, we reported the first allylic decarboxylation reaction of pentadienyl esters.[56] We considered that the pentadienyl group was assisting with reactivity so it was believed that the palladium-catalyzed decarboxylation of diester **2.73** would be as successful as the previous example. Interestingly, when saturated diester **2.73** was subjected to the same decarboxylation conditions as those published for the synthesis of clinprost (**2.3**), the expected product was not observed. Multiple trials using more forcing conditions were conducted and all yielded the same result; the starting material rearranged to the linear pentadienyl ester but did not undergo decarboxylation. This result gave further evidence to the uniqueness of the previously described decarboxylation that will be discussed in greater detail in the following section.

5. Exploration into the Novel Decarboxylation Reaction

Decarboxylation reactions have a rich history in organic synthesis, including syntheses of cubane and morphine (Figure 2.8).[69] However, classical decarboxylations typically use high temperatures and/or strong acids or bases.[70–72] In more recent years, many metal-catalyzed decarboxylations have been reported (Figure 2.8)[62] with less harsh conditions, although anion-stabilizing groups are still required. As mentioned earlier, we have demonstrated that bis-allylic dienoate systems could be decarboxylated with the bis-allylic group rearranging to a linear pentadienyl moiety. It was also found later that this decarboxylation can take place at room temperature instead of heating to 50 °C and without the need of an anion-stabilizing group (Figure 2.10). Due to the potential impact of the decarboxylative coupling observed, we decided to study the reaction further.

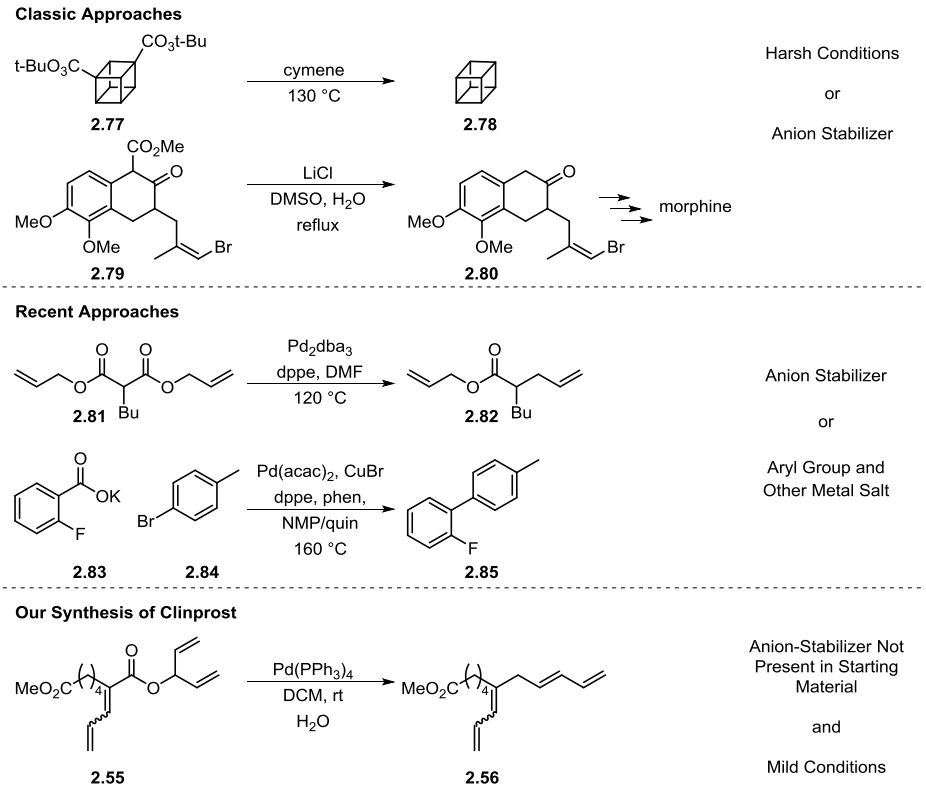
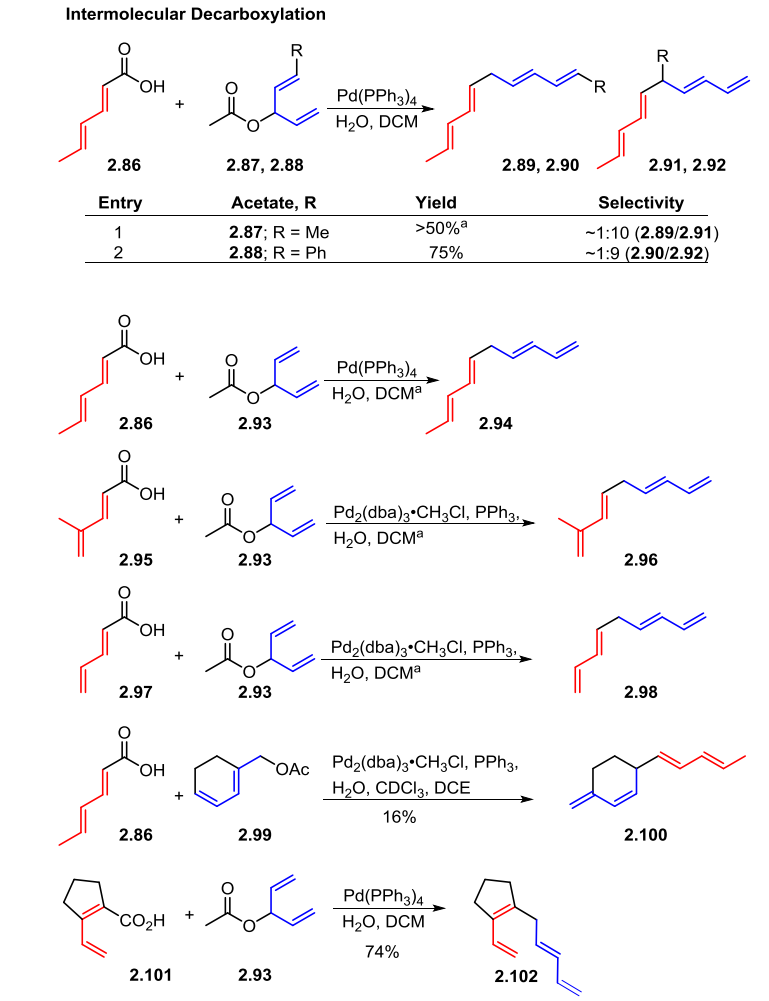


Figure 2.8. Examples of Decarboxylation Reactions.

The $Pd(PPh_3)_4$ catalyst was used for the model system (Scheme 2.5) as it is the most common Pd(0) source used in literature. It was then determined that phosphine ligands are required for the reaction since $Pd_2(dba)_3 \cdot CHCl_3$ was an inactive catalyst until PPh_3 was added into the reaction mixture. Another aspect to this system is the importance of water for the reaction. Originally, we found that a fresh bottle of $Pd(PPh_3)_4$ had lower yields than an older bottle. After screening a variety of impurities, including triphenylphosphine oxide, we found that when one equivalent of water was added to the reaction, decarboxylation was once again achieved. Other protic sources (e.g. TFE, MeOH, *t*BuOH) had similar effects; however, H_2O was superior. Different solvents were

screened, including THF, DMF, DMSO, toluene and others, to show that DCM or chloroform work optimally for the novel decarboxylation.

Further examples illustrating the usefulness of this novel decarboxylation, were developed by modifying the dienoate and pentadienyl groups (Scheme 2.16). Surprisingly, these reactions can be performed intramolecularly or intermolecularly. Screening different groups, such as alkenes, aromatics, cyclopropanes, alkynes and alkanes, instead of dienoate or pentadienyl groups, demonstrated that all these moieties failed to decarboxylate. This shows that both the diene and pentadienyl systems are required for the novel decarboxylation (Figure 2.9).



Entry	Acetate, R	Yield	Selectivity
1	**2.87**; R = Me	>50%[a]	~1:10 (**2.89**/**2.91**)
2	**2.88**; R = Ph	75%	~1:9 (**2.90**/**2.92**)

[a]yield not determined due to volatility

Scheme 2.16. Examples of Alkylative Inter- and Intramolecular Decarboxylations.

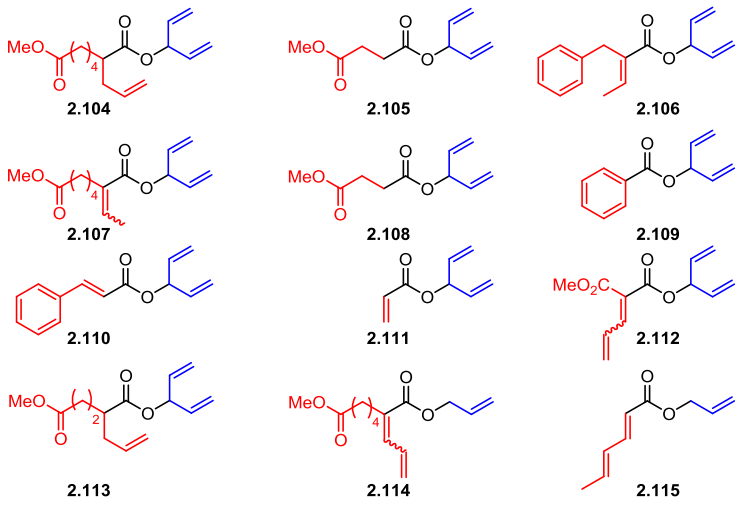


Figure 2.9. Unsuccessful Substrates for Decarboxylation.

As noticed from the unsuccessful substrates of this novel decarboxylation (Figure 2.9), this reaction requires the presence of both the dienoate and pentadienyl groups to work. Although many substrates failed to decarboxylate, these results gave us insights into the structural constraints of the process. Future efforts will be focused, on experimental and computational evaluation of potential mechanisms for the reaction using our current results as a guide.

6. Conclusion

The total synthesis of clinprost (**2.3**) in nine total steps and analogues synthesis in seven total steps is described utilizing inexpensive and commercially available starting materials (Figure 2.10). Although the first two approaches failed, we developed and designed two new reactions for the successful synthetic route: a decarboxylation of pentadienyl dienoate systems and a [2+2+1] cycloaddition of bis-diene systems. These

new reactions led to a rapid increase in the molecular complexity to afford the bicyclic core with four stereocenters as desired. This bicyclic core was used in a late-stage cross metathesis reaction to synthesize analogues with different ω-sidechains and to decrease the total number of steps to nine or fewer steps instead of 15 or more steps in previous syntheses. Some of the analogues had more simplified sidechains, which further shortened the synthetic route. We are currently exploring the synthesis of future analogues based on the same bicyclic core. Furthermore, the developed novel decarboxylation is being seperatly optimized to be used for the synthesis of other pentadienoate substrates.

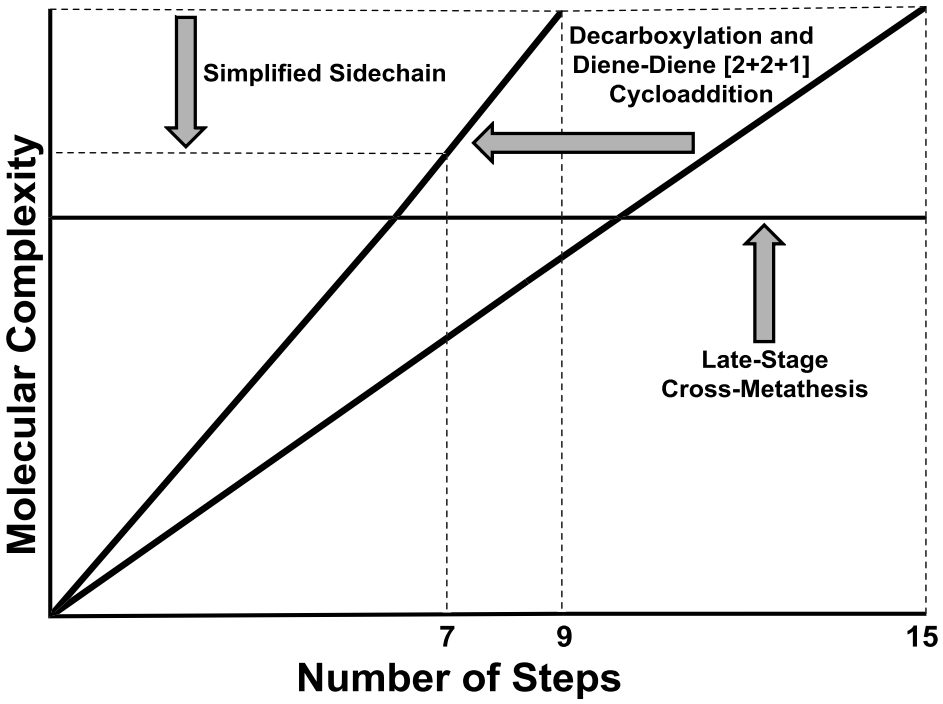


Figure 2.10. Utilization of Step-Saving Techniques in the Synthesis of Clinprost and Simplified Analogues.

7. References

1. Nicolaou, K. C.; Montagnon, T. *Molecules that changed the world: a brief history of the art and science of synthesis and its impact on society*; Wiley-VCH: Weinheim, **2008**.

2. Gates, M.; Tschudi, G. *J. Am. Chem. Soc.* **1956**, *78*, 1380–1393.

3. Woodward, R. B.; Cava, M. P.; Ollis, W. D.; Hunger, A.; Daeniker, H. U.; Schenker, K. *J. Am. Chem. Soc.* **1954**, *76*, 4749–4751.

4. Knight, S. D.; Overman, L. E.; Pairaudeau, G. *J. Am. Chem. Soc.* **1995**, *117*, 5776–5788.

5. Stork, G.; Niu, D.; Fujimoto, A.; Koft, E. R.; Balkovec, J. M.; Tata, J. R.; Dake, G. R. *J. Am. Chem. Soc.* **2001**, *123*, 3239–3242.

6. Woodward, R. B.; Doering, W. E. *J. Am. Chem. Soc.* **1945**, *67*, 860–874.

7. Holton, R. A.; Kim, H. B.; Somoza, C.; Liang, F.; Biediger, R. J.; Boatman, P. D.; Shindo, M.; Smith, C. C.; Kim, S. *J. Am. Chem. Soc.* **1994**, *116*, 1599–1600.

8. Nicolaou, K. C.; Yang, Z.; Liu, J. J.; Ueno, H.; Nantermet, P. G.; Guy, R. K.; Claiborne, C. F.; Renaud, J.; Couladouros, E. A.; Paulvannan, K.; Sorensen, E. J. *Nature* **1994**, *367*, 630–634.

9. Ojima, I.; Habus, I.; Zhao, M.; Zucco, M.; Park, Y. H.; Sun, C. M.; Brigaud, T. *Tetrahedron* **1992**, *48*, 6985–7012.

10. Wender, P. A.; Badham, N. F.; Conway, S. P.; Floreancig, P. E.; Glass, T. E.; Houze, J. B.; Krauss, N. E.; Lee, D.; Marquess, D. G.; McGrane, P. L.; Meng, W.; Natchus, M. G.; Shuker, A. J.; Sutton, J. C.; Taylor, R. E. *J. Am. Chem. Soc.* **1997**, *119*, 2757–2758.

11. Mukaiyama, T.; Shiina, I.; Iwadare, H.; Saitoh, M.; Nishimura, T.; Ohkawa, N.; Sakoh, H.; Nishimura, K.; Tani, Y.; Hasegawa, M.; Yamada, K.; Saitoh, K. *Chem. – Eur. J.* **1999**, *5*, 121–161.

12. Kusama, H.; Hara, R.; Kawahara, S.; Nishimori, T.; Kashima, H.; Nakamura, N.; Morihira, K.; Kuwajima, I. *J. Am. Chem. Soc.* **2000**, *122*, 3811–3820.

13. Corey, E. J. *Angew. Chem. Int. Ed Engl.* **2002**, *41*, 1650–1667.

14. Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127–2129.

15. Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974–5976.

16. Noyori, R.; Ohkuma, T.; Kitamura, M.; Takaya, H.; Sayo, N.; Kumobayashi, H.; Akutagawa, S. *J. Am. Chem. Soc.* **1987**, *109*, 5856–5858.

17. Wender, P. A.; Verma, V. A.; Paxton, T. J.; Pillow, T. H. *Acc. Chem. Res.* **2008**, *41*, 40–49.

18. Wender, P. A.; Croatt, M. P.; Witulski, B. *Tetrahedron* **2006**, *62*, 7505–7511.

19. Newhouse, T.; Baran, P. S.; Hoffmann, R. W. *Chem. Soc. Rev.* **2009**, *38*, 3010–3021.

20. Trost, B. M. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 259–281.

21. Wender, P. A.; Handy, S. T.; Wright, D. L. *ResearchGate* **1997**, X–XI.

22. Chanon, M.; Barone, R.; Baralotto, C.; Julliard, M.; Hendrickson, J. B. *Synth. Stuttg.* **1998**, 1559–1583.

23. Reppe, W.; Schlichting, O.; Klager, K.; Toepel, T. *Justus Liebigs Ann. Chem.* **1948**, *560*, 1–92.

24. Wender, P. A.; Ternansky, R. J. *Tetrahedron Lett.* **1985**, *26*, 2625–2628.

25. Willstätter, R.; Waser, E. *Berichte Dtsch. Chem. Ges.* **1911**, *44*, 3423–3445.

26. Barone, R.; Chanon, M. *Tetrahedron* **2005**, *61*, 8916–8923.

27. Strader, C. R.; Pearce, C. J.; Oberlies, N. H. *J. Nat. Prod.* **2011**, *74*, 900–907.

28. Adachi K; Chiba K *Perspect. Med. Chem.* **2008**, *1*, 11–23.

29. Ganem, B.; Franke, R. R. *J. Org. Chem.* **2007**, *72*, 3981–3987.

30. Pazdur, R.; Kudelka, A. P.; Kavanagh, J. J.; Cohen, P. R.; Raber, M. N. *Cancer Treat. Rev.* **1993**, *19*, 351–386.

31. Whittaker, N.; Bunting, S.; Salmon, J.; Moncada, S.; Vane, J. R.; Johnson, R. A.; Morton, D. R.; Kinner, J. H.; Gorman, R. R.; McGuire, J. C.; Sun, F. F. *Prostaglandins* **1976**, *12*, 915–928.

32. Kermode, J.; Butt, W.; Shann, F. *Br. Heart J.* **1991**, *66*, 175–178.

33. Funk, C. D. *Science* **2001**, *294*, 1871–1875.

34. Capra, V.; Bäck, M.; Barbieri, S. S.; Camera, M.; Tremoli, E.; Rovati, G. E. *Med. Res. Rev.* **2013**, *33*, 364–438.

35. Ishikawa, T.; Ishii, H.; Shimizu, K.; Nakao, H.; Urano, J.; Kudo, T.; Saito, S. *J. Org. Chem.* **2004**, *69*, 8133–8135.

36. Shibasaki, M.; Torisawa, Y.; Ikegami, S. *Tetrahedron Lett.* **1983**, *24*, 3493–3496.

37. O'Grady, J.; Hedges, A.; Whittle, B.; Al-Sinawi, L.; Mekki, Q.; Burke, C.; Moody, S.; Moti, M.; Hassan, S. *Br. J. Clin. Pharmacol.* **1984**, *18*, 921–933.

38. Matsuda, S.; Wen, T.-C.; Karasawa, Y.; Araki, H.; Otsuka, H.; Ishihara, K.; Sakanaka, M. *Brain Res.* **1997**, *769*, 321–328.

39. Takamatsu, H.; Tsukada, H.; Watanabe, Y.; Cui, Y.; Kataoka, Y.; Hosoya, T.; Suzuki, M.; Watanabe, Y. *Brain Res.* **2002**, *925*, 176–182.

40. Cui Y; Takamatsu H; Kakiuchi T; Ohba H; Kataoka Y; Yokoyama C; Onoe H; Watanabe Y; Hosoya T; Suzuki M; Noyori R; Tsukada H; Watanabe Y *Stroke J. Cereb. Circ.* **2006**, *37*, 2830–6.

41. Yae T; Araki H; O-ogami Y; Iwasaki K; Tanabe H; Fujiwara M *Arzneimittelforschung.* **1997**, *47*, 1200–3.

42. Lutsep, H. L.; Clark, W. M. *Formulary* **1997**, *32*, 1040–1047.

43. Suzuki, M.; Kato, K.; Noyori, R.; Watanabe, Y.; Takechi, H.; Matsumura, K.; Långström, B.; Watanabe, Y. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 334–336.

44. Suzuki, M.; Kato, K.; Noyori, R.; Watanabe, Y.; Satoh, T.; Matsumura, K.; Watanabe, Y. *Chem. Commun.* **1999**, 307–308.

45. Satoh, T.; Ishikawa, Y.; Kataoka, Y.; Cui, Y.; Yanase, H.; Kato, K.; Watanabe, Y.; Nakadate, K.; Matsumura, K.; Hatanaka, H.; Kataoka, K.; Noyori, R.; Suzuki, M.; Watanabe, Y. *Eur. J. Neurosci.* **1999**, *11*, 3115–3124.

46. Donnan, G. A.; Fisher, M.; Macleod, M.; Davis, S. M. *The Lancet* **2008**, *371*, 1612–1623.

47. Mozaffarian, D.; Benjamin, E. J.; Go, A. S.; Arnett, D. K.; Blaha, M. J.; Cushman, M.; Ferranti, S. de; Després, J.-P.; Fullerton, H. J.; Howard, V. J.; Huffman, M. D.; Judd, S. E.; Kissela, B. M.; Lackland, D. T.; Lichtman, J. H.; Lisabeth, L. D.; Liu, S.; Mackey,

R. H.; Matchar, D. B.; McGuire, D. K.; Mohler, E. R.; Moy, C. S.; Muntner, P.; Mussolino, M. E.; Nasir, K.; Neumar, R. W.; Nichol, G.; Palaniappan, L.; Pandey, D. K.; Reeves, M. J.; Rodriguez, C. J.; Sorlie, P. D.; Stein, J.; Towfighi, A.; Turan, T. N.; Virani, S. S.; Willey, J. Z.; Woo, D.; Yeh, R. W.; Turner, M. B. *Circulation* **2015**, *131*, e29–e322.

48. Plum F *JAMA* **2001**, *285*, 1760–1761.

49. Carden, D. L.; Granger, D. N. *J. Pathol.* **2000**, *190*, 255–266.

50. Hashimoto, S.; Shinoda, T.; Ikegami, S. *J. Chem. Soc. Chem. Commun.* **1988**, 1137–1139.

51. Hashimoto, S.; Shinoda, T.; Shimada, Y.; Honda, T.; Ikegami, S. *Tetrahedron Lett.* **1987**, *28*, 637–640.

52. Sodeoka, M.; Ogawa, Y.; Mase, T.; Shibasaki, M. *Chem. Pharm. Bull. (Tokyo)* **1989**, *37*, 586–598.

53. Bannai, K.; Tanaka, T.; Okamura, N.; Hazato, A.; Sugiura, S.; Manabe, K.; Tomimori, K.; Kurozumi, S. *Tetrahedron Lett.* **1986**, *27*, 6353–6356.

54. Graul, A.; Leeson, P.; Castaner, J. *Drug Future* **1997**, *22*, 608.

55. Tanaka, T.; Bannai, K.; Hazato, A.; Koga, M.; Kurozumi, S.; Kato, Y. *Tetrahedron* **1991**, *47*, 1861–1876.

56. Nagy, E. E.; Hyatt, I. F. D.; Gettys, K. E.; Yeazell, S. T.; Frempong, S. K.; Croatt, M. P. *Org. Lett.* **2013**, *15*, 586–589.

57. Sheddan, N. A.; Mulzer, J. *Org. Lett.* **2006**, *8*, 3101–3104.

58. Croatt, M. P.; Wender, P. A. *Eur. J. Org. Chem.* **2010**, *2010*, 19–32.

59. Voss, G.; Gerlach, H. *Helv. Chim. Acta* **1983**, *66*, 2294–2307.

60. Yus, M.; Torregrosa, R.; Pastor, I. M. *Molecules* **2004**, *9*, 330–348.

61. Appel, R. *Angew. Chem. Int. Ed. Engl.* **1975**, *14*, 801–811.

62. Weaver, J. D.; Recio, A.; Grenning, A. J.; Tunge, J. A. *Chem. Rev.* **2011**, *111*, 1846–1913.

63. Rodríguez, N.; Goossen, L. J. *Chem. Soc. Rev.* **2011**, *40*, 5030–5048.

64. Grilli, S.; Martelli, G.; Savoia, D. *Eur. J. Org. Chem.* **2001**, *2001*, 2917–2922.

65. Wender, P. A.; Croatt, M. P.; Deschamps, N. M. *J. Am. Chem. Soc.* **2004**, *126*, 5948–5949.

66. Wender, P. A.; Deschamps, N. M.; Gamber, G. G. *Angew. Chem. Int. Ed Engl.* **2003**, *42*, 1853–1857.

67. Wender, P. A.; Croatt, M. P.; Deschamps, N. M. *Angew. Chem. Int. Ed Engl.* **2006**, *45*, 2459–2462.

68. Felluga, F.; Forzato, C.; Ghelfi, F.; Nitti, P.; Pitacco, G.; Pagnoni, U. M.; Roncaglia, F. *Tetrahedron Asymmetry* **2007**, *18*, 527–536.

69. Jordan, F.; Patel, H. *ACS Catal.* **2013**, *3*, 1601–1617.

70. Barborak, J. C.; Watts, L.; Pettit, R. *J. Am. Chem. Soc.* **1966**, *88*, 1328–1329.

71. Wiberg, K. B.; Lowry, B. R.; Colby, T. H. *J. Am. Chem. Soc.* **1961**, *83*, 3998–4006.

72. Taber, D. F.; Neubert, T. D.; Rheingold, A. L. *J. Am. Chem. Soc.* **2002**, *124*, 15399–15399.

CHAPTER III

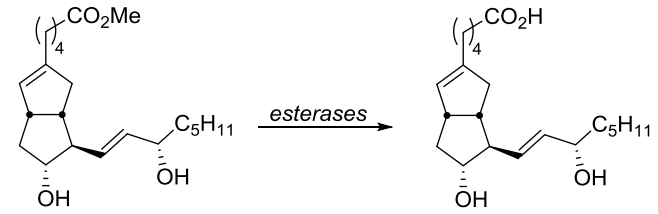
SYNTHESIS AND BIOLOGICAL EVALUATION OF NEUROPROTECTIVE AGENTS AGAINST STROKE

1. Background and Significance

Stroke is one of the leading causes of death and has been known to cause serious injuries to many people.[1] Each year around 800,000 people in the United States have a new or recurrent stroke according to the statistics compiled by researchers of the American Heart Asssociation.[2] On average someone dies every 4 minutes in the United States because of stroke. Between the two types of stroke, hemorrhagic and ischemic, ischemic stroke accounts for the majority with about 87% of the strokes.[2–4] Ischemic stroke is caused by occlusion of a blood vessel in the brain which leads to reduced blood supply and availability of oxygen and glucose to the affected area in the brain.[5,6] This deprivation in blood flow is followed by a dilation of blood vessels around the ischemic area to restore blood flow that is followed with a rapid influx of reactive oxygen species, a process known as reperfusion.[6–10] This places the neuronal cells at a risk of further damage and limits their recovery.

Despite decades of research, treatment options for ischemic stroke remain limited. Currently the only FDA-approved ischemic stroke therapy is tissue plasminogen activator, also known as Activase®, which has a limited time window.[6,7] Other medicines

that are available in the market are only used as preventative therapies for protection against platelet aggregation, such as clopidogrel or against blood clotting such as warfarin. Therefore, the search for novel therapeutics that have the potential to protect brain tissue from this damage is urgent.[6,10] Two of the promising neuroprotective agents are isocarbacyclin (**3.2**) and clinprost (**3.1**). Clinprost (**3.1**) is the methyl ester of isocarbacyclin (**3.2**) and found to be hydrolyzed by esterases in the brain to form isocarbacyclin (**3.2**; Scheme 3.1).[11] They are both chemically stable prostaglandin analogues (PGI_2)[12] and are found to have a highly potent neuroprotective effect against ischemic stroke in animal models by increasing the blood flow in the ischemic area and preventing platelets aggregation.[7,11,13–16]



Clinprost, **3.1** Isocarbacyclin, **3.2**

Scheme 3.1. Clinprost (**3.1**) Hydrolyzes to Isocarbacyclin (**3.2**) in Brain.

A significant amount of research on neuroprotection against ischemic stroke has been performed using animal models. One of the studies for the neuroprotective effect of isocarbacyclin (**3.2**) against neuronal damage in gerbils demonstrated that it prevents the occurrence of neuronal damage after an induced ischemic stroke.[12] In this study, they infused saline (vehicle), isocarbacyclin (**3.2**, 0.12 ng/day) or isocarbacyclin (**3.2**, 1.2 ng/day) for 7 days into gerbils' brains starting 3-minutes after the induced ischemic

stroke (Figure 3.1). It was found that there was a significant difference in the neuronal density between the vehicle and isocarbacyclin infusion (**3.2**, 1.2 ng/day) with 137 cells/mm and 197 cell/mm respectively (Figure 3.1). This indicated that the treatment with isocarbacyclin (**3.2**) had significant results in preventing the ischemia.

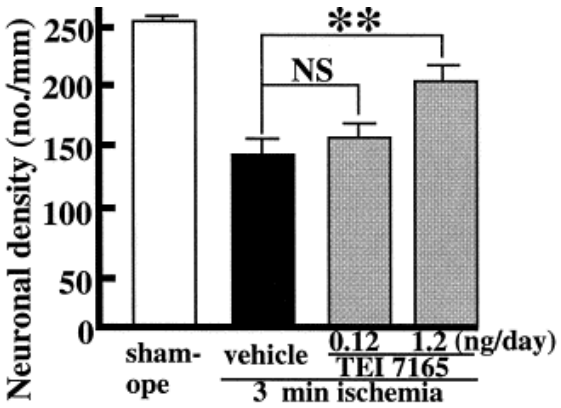


Figure 3.1. Effects of Isocarbacyclin (**3.2**, TEI 7165) on Neuronal Density of the Brain Region in Gerbils with 3-min Forebrain Ischemia. This graphic was reproduced with a permission from Elsevier.[12]

Another part of the study showed photomicrographs of a normal brain of gerbils (Figure 3.2; A), an ischemic brain with a vehicle infusion (Figure 3.2; B) and an ischemic brain with isocarbacyclin infusion (Figure 3.2; C), which significantly shows the neuroprotection effect of isocarbacyclin (**3.2**) on a gerbil neuronal cells after an induced ischemic stroke.

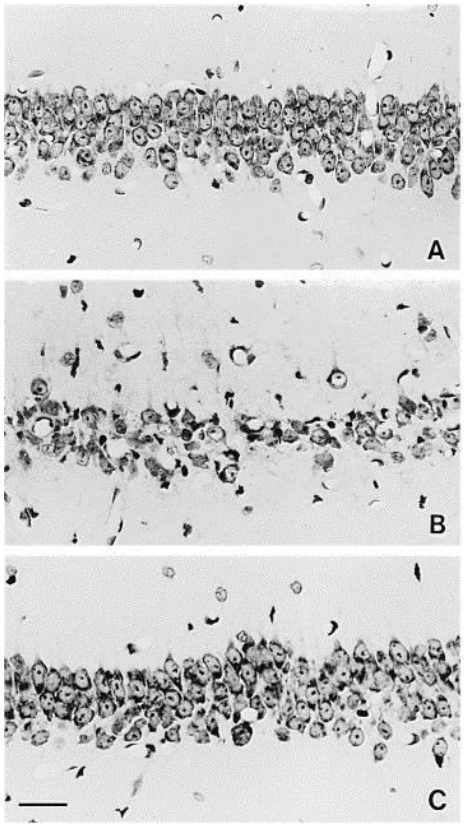


Figure 3.2. Photomicrographs of a Gerbil Brain with or without 3-min Ischemia. A: Normal Animal with Vehicle Infusion. B: Ischemic Animal with Vehicle Infusion. C: Ischemic Animal with isocarbacyclin (**3.2**) (1.2 ng/day) infusion. This graphic was reproduced with permission from Elsevier.[12]

A few studies showed that isocarbacyclin (**3.2**) was found to have a great potency to a subtype prostaglandin receptor (prostacyclin receptor), IP_2, that is expressed in the central nervous system and distinguished from the peripheral type receptor, IP_1, found in the peripheral nervous system.[7,8,16–18] This finding is in agreement with the neuroprotection action of isocarbacyclin (**3.2**), however the mechanism of the IP_2 receptor ligand has not been clarified. The biological activity of this promising compound

has been only limited to few studies which were performed on animal models due to its complex structure that limited its synthesis. The Croatt research group reported the synthesis of clinprost (**3.1**) in only 9 steps,[19,20] as will be described herein, which has been used in the synthesis of clinprosts' free acid, isocarbacyclin (**3.2**), and its analogues in 10 or fewer steps.

2. Results and Discussion

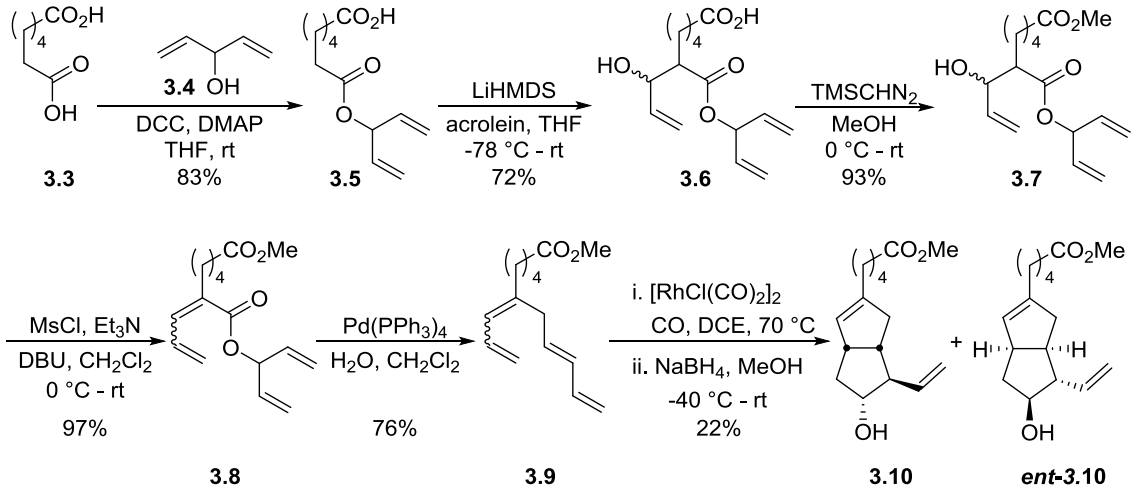
2.1 Synthesis of Isocarbacyclin and Analogues

Having this valuable biological activity, clinprost and isocarbacyclin were synthesized by several groups with diverse approaches, however, most were 20 or more steps with the shortest reported synthesis requiring 15 steps starting from commercially available materials.[21–30] Isocarbacyclin and other analogues were synthesized, as will be described herein, by coupling different alkenes to the same bicyclic building block (**3.10**; Scheme 3.2), which was made in only 6 steps from commercially available materials. This route design allowed for a late-stage diversification by using a cross-metathesis reaction.

2.1.1 Synthesis of Bicyclic Core (3.10)

The step-economical synthesis of clinprost (**3.1**) reported by the Croatt group[19,20] has been used to make isocarbacyclin and other analogues having different ω-side chains from the same bicyclic core (**3.10**; Scheme 3.2). The synthesis of the core begins with reacting excess pimelic acid (**3.3**) with bisallylic alcohol (**3.4**) to get monoester **3.5** as a major product followed by aldol condensation with acrolein. A limitation in the second

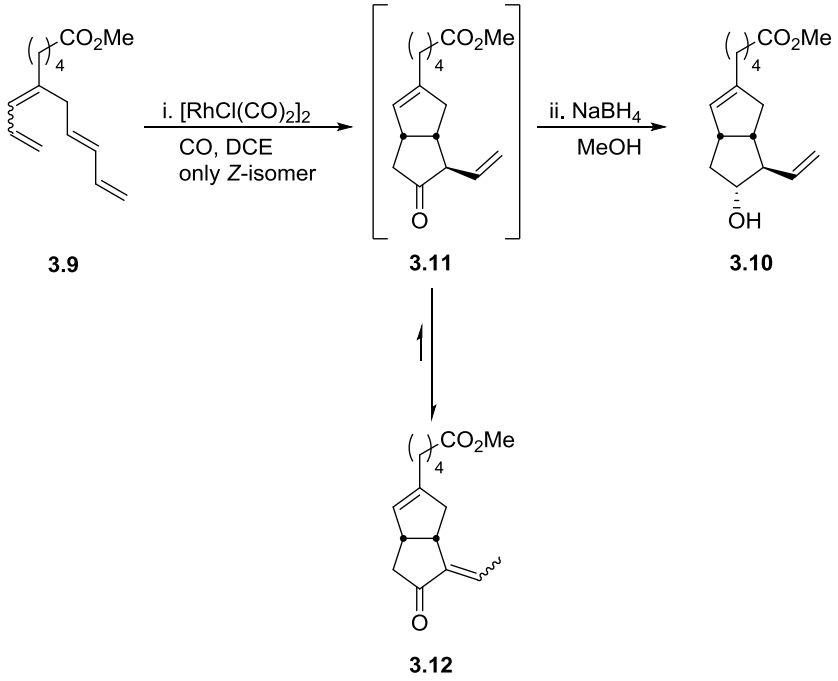
step was the quick polymerization of acrolein during the reaction workup and purification. Prior researchers in our group tried various conditions to find that using LiHMDS in THF as a base gave the maximum yield of 15%. Later we found that using solid LiHMDS increased the yield to 72%.



Scheme 3.2. Synthesis of the Bicyclic Core (**3.10**).

The resulting acid (**3.6**) was subjected to methylation and dehydration to get ester (**3.8**) that was subjected to Pd^0 which results in a simultaneous decarboxylation of the allyl ester and allylic rearrangement to form tetraene (**3.9**). This new type of decarboxylation was studied in more detail as will be described later (Chapter IV). Tetraene (**3.9**) is then reacted with a Rh^I catalyst under carbon monoxide atmosphere in a bis-diene [2+2+1] cycloaddition reaction followed by an *in situ* reduction. The four stereocenters of bicycle **3.10** are set in the same manner as in isocarbacyclin (**3.2**). Although [2+2+1] reactions are known for alkynes and alkenes,[31–36] allenes and dienes,[31] or alkenes and dienes,[37,38] this is the first [2+2+1] cyclocarbonylation of tethered dienes.

However, the yield is low as only the *Z*-isomer reacts to give bicycle **3.11** while the *E*-isomer does not react. Moreover, ketone **3.11** isomerizes quickly to the more stable and undesired isomer (**3.12**, Scheme 3.3).



Scheme 3.3. Bis-diene [2+2+1] Cycloaddition Reaction.

Different conditions were screened in order to more efficiently form the desired product (**3.10**; Table 3.1). 2,2,2-Trifluoroethanol (TFE) and dichloroethane (DCE) were previously found to work well with this type of reaction.[37,38] However, using TFE as a solvent in this case gives mostly the undesired isomerized product (**3.12**) with a low selectivity compared to DCE (entries 1-6). Having DCE as a solvent, different catalytic amounts of Rh^{I} catalyst were screened to find that increasing the catalytic loading had no effect on the yield or increasing the selectivity for the desired product (**3.10**, entries 7, 8).

It was also shown that this reaction is time dependent (entries 9-12), as running the reaction in DCE and 10 mol % catalyst less than 6 hours will give only traces of the product (**3.10**) and more than 10 hours will cause the product to isomerize. Other different conditions were screened by changing the temperature and time to find that running the reaction for 8-10 hours at 70 °C provided the best yield (22%, entry 13) over the 2 steps. The yield for this step led us to develop a route for a different type of analogues where the double bond in the tetraene derivative is locked in the *Z*-form only. This will be discussed later in more details in this chapter (section 2.3).

Table 3.1. Different Conditions for [2+2+1] Cycloaddition.

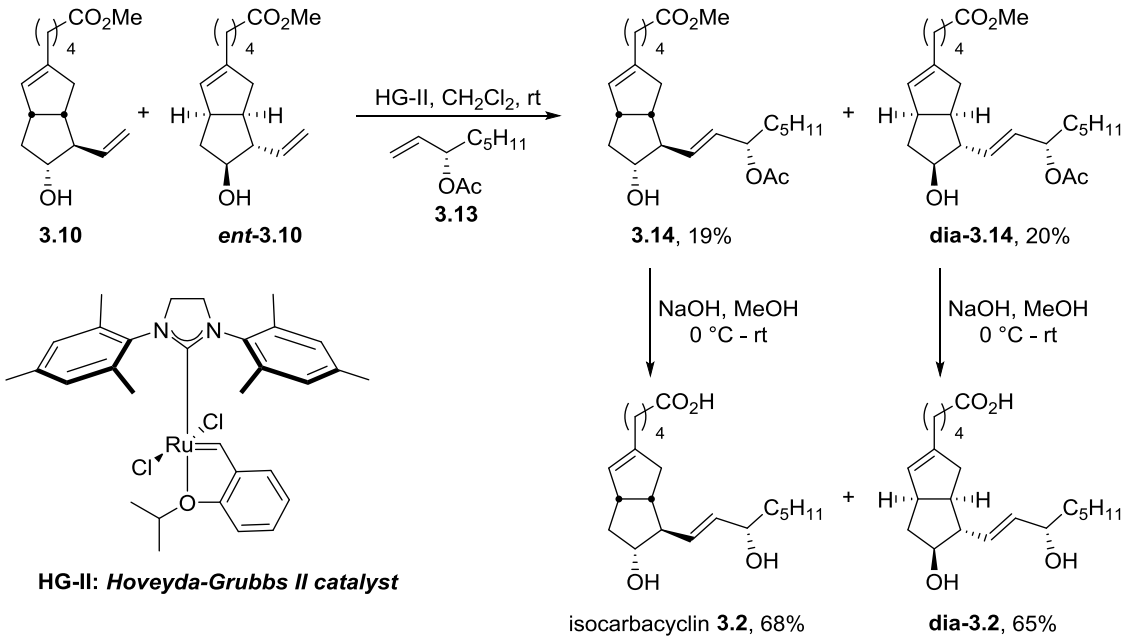
Entry	**Solvent**	**Temperature**	**Catalytic Amount**	**Time**	**Product**	**Yield of 3.10**
1	TFE	60 °C	10 mol %	40 min	**3.12**	--
2	DCE/TFE, 1:1	80 °C	10 mol %	15 min	**3.11+3.12**	Traces
3	DCE/TFE, 1:7	80 °C	10 mol %	5 min	**3.11+3.12**	Traces
4	DCE/TFE, 1:9	80 °C	15 mol %	7 min	**3.11+3.12**	8%
5	DCE/TFE, 1:9	80 °C	20 mol %	10 min	**3.12**	--
6	DCE/TFE,	80 °C	10 mol %	3 hr	**3.11+3.12**	Traces

	10:1					
7	DCE	80 °C	10 mol %	8 hr	**3.11+3.12**	11%
8	DCE	80 °C	25 mol %	8 hr	**3.11+3.12**	7%
9	DCE	80 °C	10 mol %	2 hr	**3.11+3.12**	Traces
10	DCE	80 °C	10 mol %	5 hr	**3.11+3.12**	Traces
11	DCE	80 °C	10 mol %	10 hr	**3.11+3.12**	9%
12	DCE	80 °C	10 mol %	overnight	**3.11+3.12**	Traces
13	DCE	70 °C	10 mol %	8 hr	**3.11+3.12**	22%

[a]Reaction Conditions: Bis-diene (**3.9**, 1eq), under CO atmosphere, in solvent (0.1 M).

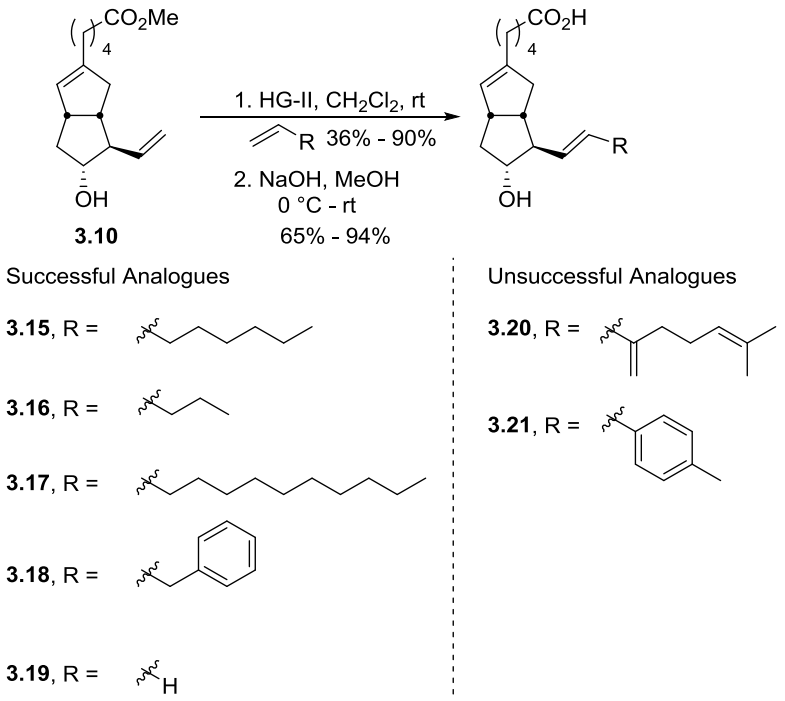
2.1.2 Synthesis of Isocarbacyclin and Analogues (3.2, 3.15 - 3.19)

To complete the synthesis of isocarbacyclin, a Ru^{II}-catalyzed cross metathesis was utilized to attach the ω-side chain, (*S*)-3-acetoxy-oct-1-ene (**3.13**), which was synthesized using an enzymatic resolution of racemic 1-octen-3-ol as shown in Chapter II, section 4.2.[28] This cross metathesis was followed by a hydrolysis using NaOH to remove the protecting groups and result in isocarbacyclin (**3.2**) and its diastereomer (**dia-3.2**) in an enantioselective fashion (Scheme 3.4). Although the hydrolysis reaction appears simple, many trials were carried out in order for the reaction to work. It was found that the resulting analogues decomposed to an unknown byproduct(s). Therefore, the reaction needs careful workup and purification to obtain the product.



Scheme 3.4. Enantioselective Synthesis of Isocarbacyclin (**3.2**) and its Diastereomer (**dia-3.2**).

A cross-metathesis approach has been successfully applied using different terminal alkenes followed by hydrolysis of the methyl ester to afford other analogues (**3.15** - **3.19**) from the same bicyclic core (**3.10**; Scheme 3.5). Moreover, bicyclic core **3.10** was directly subjected to hydrolysis since it is considered as another analogue for isocarbacyclin missing the ω-side chain. Two commercially available alkenes, *p*-styrene and myrcene, were tested in the cross metathesis as well. However, only homocoupling byproducts were observed as a result of the high conjugation and the synthesis of analogues **3.20** and **3.21** were unsuccessful.



Scheme 3.5. Successful (**3.15** - **3.19**) and Unsuccessful Analogues (**3.20** - **3.21**) of Isocarbacyclin.

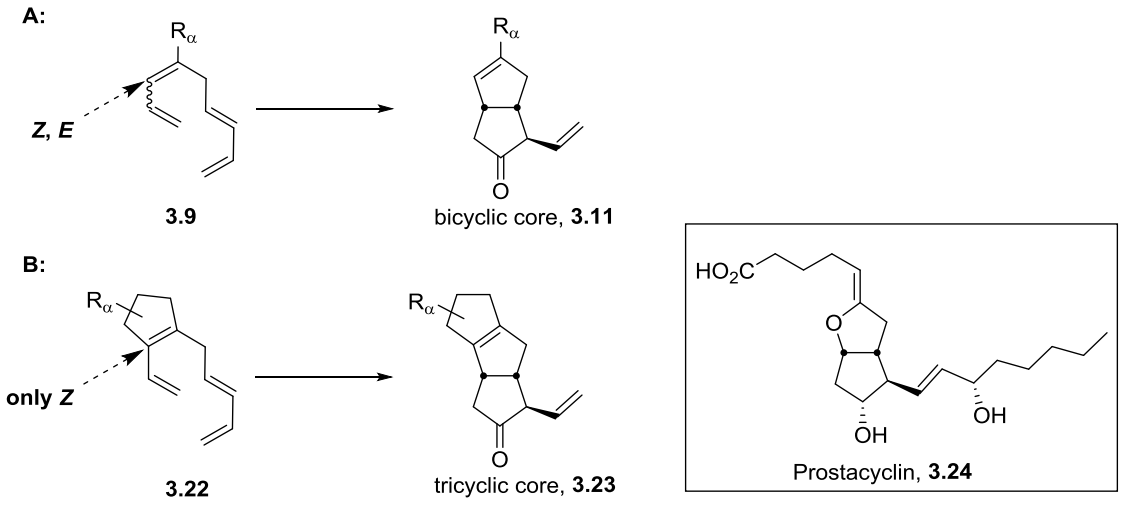
2.1.3 Biological Evaluation of Isocarbacyclin and its Bicyclic Analogues

Isocarbacyclin and bicyclic analogues (**3.2**, **3.15** - **3.19**) were sent recently to the Giffard lab, where they will be tested in a neuroprotection model using cortical neurons isolated from embryonic mouse brains. They use primary cultures to more closely approximate normal neurons than is possible using cell lines. It has previously been shown that isocarbacyclin derivatives bind to and protect certain areas of the brain, with the cortex being one of the areas where these derivatives did bind and protect from cell death.[17] The assays that the Giffard lab uses conditions that mimic ischemia. For the first assay they will examine neuroprotection from glucose deprivation, a component of ischemia which induces oxidative stress, assessing the isocarbacyclin analogues over a

range of concentrations. With the second assay, cells will be deprived of both glucose and oxygen. This is a more severe stress, which more closely mimics ischemia and reperfusion.

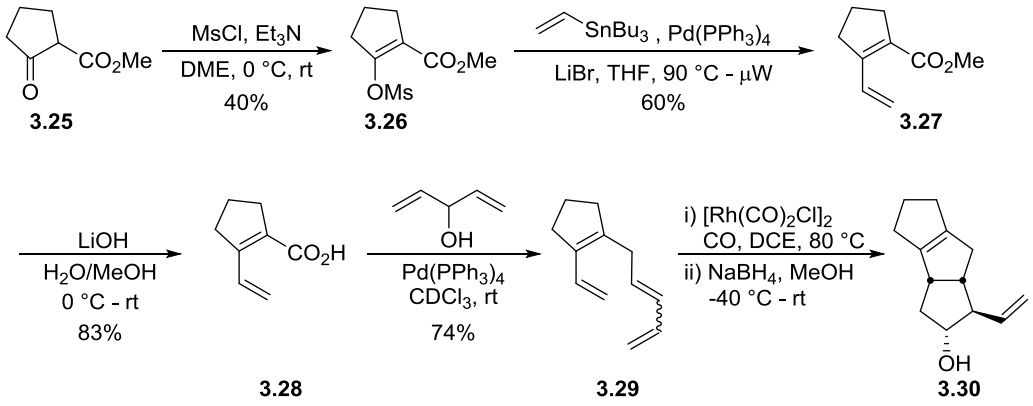
2.2 Efforts toward the Synthesis of Tricyclic Isocarbacyclin Analogues

During the synthesis of isocarbacyclin (**3.2**) and its analogues, our main focus was on optimizing the [2+2+1] cycloaddition of tetraene **3.9** that yields the bicyclic building block (**3.11**) for these analogues. We were able to maximize the yield to 22% as only the *Z*-isomer of the tetraene reacts in the cycloaddition while the *E*-isomer does not (Scheme 3.6; A). This limitation in the previous synthesis led us to design a new synthetic pathway where we can get a bis-diene with the double bond locked only in the *Z*-isomer to end up with a tricyclic core (**3.23**) for a new type of isocarbacyclin analogues (Scheme 3.6; B). Moreover the tricyclic analogues position the α-side chain in a manner similar to prostacyclin (Scheme 3.6; B).



Scheme 3.6. Bicyclic (**3.11**) vs. Tricyclic (**3.23**) Building Blocks.

A model system for the tricyclic analogues was first developed (Scheme 3.7) to test if the decarboxylation and cycloaddition reactions will be successful. The model system synthesis starts from the commercially available β-ketoester **3.25** that undergoes mesylation using MsCl to get mesylate **3.26**. Mesylate **3.26** was found to decompose on standing at ambient temperature for several hours. It was, therefore, taken directly to the Stille coupling without further purification[39] to afford dienoic ester **3.27** upon reacting with vinyl stannane.[40,41]



Scheme 3.7. Synthesis of the Tricyclic Core (**3.30**) in the Model System.

Different conditions were screened to optimize the coupling reaction (Table 3.2). The optimization started with increasing the catalytic loading of $Pd(PPh_3)_4$ from 5 mol % to 10 mol % (entries 1, 2) with no significant changes on the yield. On the other hand, a minor change on the yield was noticed when increasing the equivalents of vinyl stannane from 1.5 to 2.0 equivalents (entries 3-4). Increasing the equivalents of LiBr (entry 5) was found to decrease the yield. Having the equivalents of the reactants and catalyst optimized, different temperatures were screened using the microwave reaction (entries 6-

7) to find a huge effect when running the reaction at 90 °C to get a yield of 60%. Higher temperatures (entry 8) caused decomposition of the mesylate faster than the formation of the product.

Table 3.2. Different Conditions for the Stille Coupling.[a]

Entry	Pd^0	Vinyl Stannane	LiBr	Temperature	Yield
1	5 mol %	1.2 eq	1.5 eq	reflux	10%
2	10 mol %	1.2 eq	1.5 eq	reflux	12%
3	5 mol %	1.5 eq	1.5 eq	reflux	15%
4	5 mol %	2.0 eq	1.5 eq	reflux	20%
5	5 mol %	2.0 eq	2.0 eq	reflux	traces
6	5 mol %	2.0 eq	1.5 eq	microwave - 80 °C	42%
7	5 mol %	2.0 eq	1.5 eq	microwave - 90 °C	60%
8	5 mol %	2.0 eq	1.5 eq	microwave - 100 °C	17%

[a]Reaction Conditions: Mesylate (**3.26**, 1eq), in THF (0.1 M).

The resulting ester (**3.27**) from the Stille coupling was then subjected to hydrolysis with LiOH to afford dienoic acid (**3.28**). A one-pot reaction for Stille coupling and hydrolysis was successful to yield dienoic acid **3.28**, however, many trials to purify this compound using different solvents were unsuccessful because of streaking of the stannane byproduct. Dienoic acid **3.28** can undergo a decarboxylative coupling with

bisallylic alcohol (**3.4**) when subjected to Pd^0 conditions. The decarboxylated product (**3.29**) was subjected to Rh^I catalyst under a carbon monoxide atmosphere with several different conditions to yield only traces of tricycle **3.30** (Table 3.3). Tricycle (**3.30**) was not fully characterized due to the volatility of the starting material and the isomerization of the product; however it was clear that both reactions, decarboxylation and cycloaddition, were successful which validated moving from the model system to the real synthetic route for the tricyclic analogues.

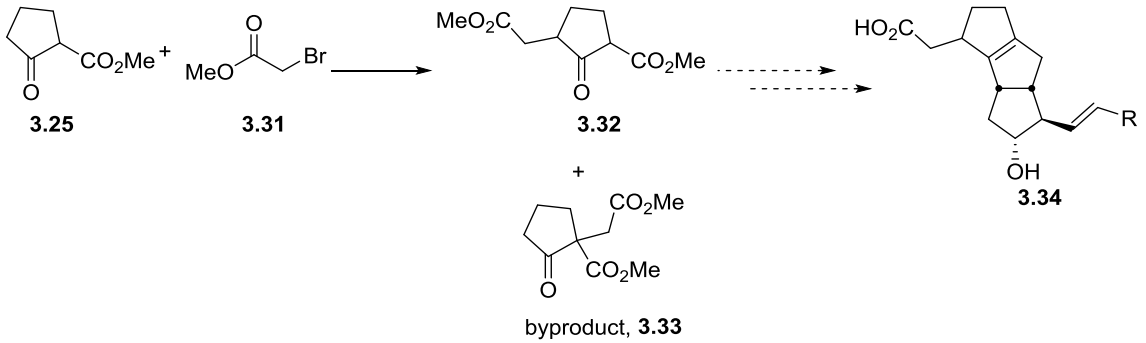
Table 3.3. Different Conditions for Cycloaddition of Tetraene (**3.29**).[a]

Entry	Catalyst	Temp	Additives	Results
1	$[RhCl(CO)_2]_2$, 10 mol %	80 °C	--	no reaction
2	$[RhCl(CO)_2]_2$, 20 mol %	80 °C	--	traces[b]
3	$[RhCl(CO)_2]_2$, 20 mol %	rt	$AgSbF_6$, 10 mol %	no reaction
4	$[RhCl(CO)_2]_2$, 20 mol %	80 °C	$AgSbF_6$, 10 mol %	traces
5	$RhCl(CO)(PPh_3)_2$, 20 mol %	80 °C	$AgSbF_6$, 10 mol %	traces

[a]Reaction Conditions: Tetraene (**3.29**, 1 eq), under CO atmosphere, in DCE (0.1 M). [b]The majority of the staring material was recovered.

Having the model system working, a synthetic scheme was proposed (Scheme 3.8) that starts with reacting β-keto ester (**3.25**) with methyl bromoacetate (**3.31**) in order to get diester (**3.32**) where this forms the α-side chain of the final analogues. Multiple conditions were attempted for this reaction with no product observed (Table 3.4). The

reactions resulted in either an unknown byproduct or the methyl acetate group added α to the ester functionality (**3.33**).



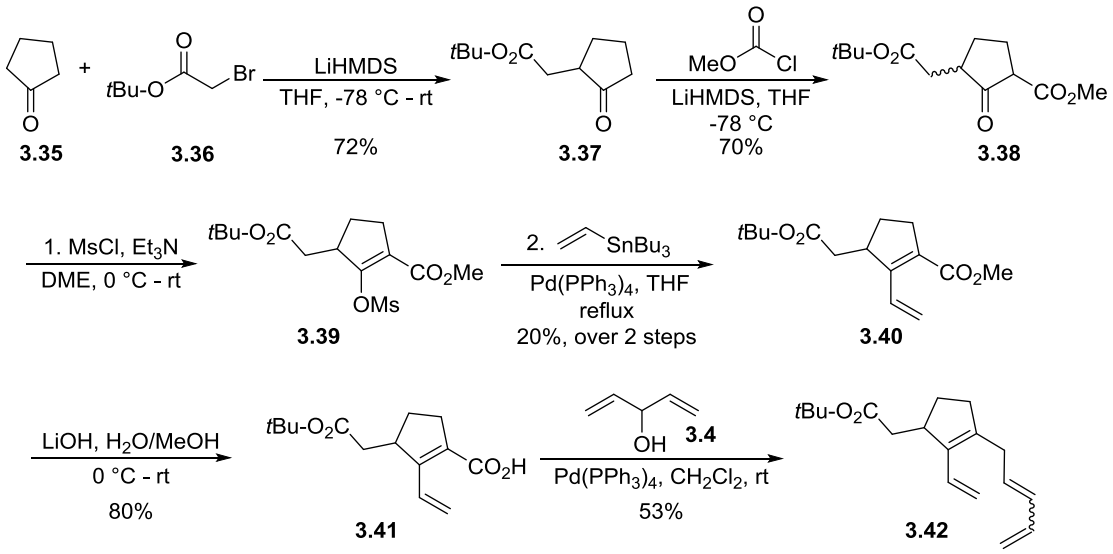
Scheme 3.8. First Proposed Synthesis for the Tricyclic Isocarbacyclin Analogues.

Table 3.4. Different Conditions for the First Step in the Tricyclic Isocarbacyclin Analogues Synthesis.[a]

Entry	Base	Temperature	Time[b]	Results
1	LiHMDS (2 eq)	-78 °C	20 min	Unknown byproduct
2	NaH (1 eq) + LiHMDS (1 eq)	-78 °C - rt	20 min	Unknown byproduct
3	LiHMDS (2 eq)	-78 °C	20 min	**3.33**
4	KHMDS (2 eq)	-78 °C	20 min	**3.33**
5	KHMDS (2 eq)	-78 °C	2 hr	**3.33**
6	KHMDS (2 eq)	-78 °C - rt	2 hr	No reaction

[a]Reaction Conditions: β-keto ester (**3.25**, 1 eq), methyl bromoacetate (**3.31**, 1 eq), in THF (0.1 M). [b]Time before the addition of **3.31**.

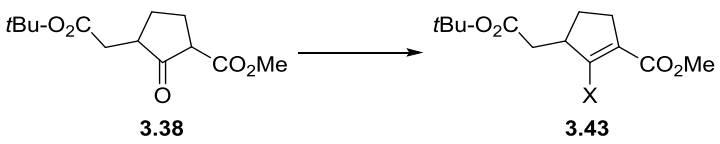
Another synthetic scheme for the tricyclic core (**3.34**) was developed after the first step failed in the previous synthesis (Scheme 3.9). For this synthesis, we tried to attach the acetyl functionality before the methyl ester group; cyclopentanone (**3.35**) was reacted with *t*-butyl bromoacetate (**3.36**) to afford ketone **3.37**. Ketone **3.37** then reacts with methyl chloroformate, using LiHMDS as a base to provide diester **3.38**. After a few trials changing the time for this reaction and getting an unknown byproduct in this step, it was found that leaving the reaction to warm to room temperature for more than four hours will cause the decomposition of the product to an unknown byproduct. As a result, the reaction was left in the cooling bath for four hours to optimally synthesize the diester (**3.38**). In this way, we were able to get the analogues similar to the previous synthesis. As a difference the structure has two orthogonal carboxylic acid protecting groups, which make it beneficial for this route later, as we can selectively hydrolyze one of them.



Scheme 3.9. Synthesis of Tetraene Building Block (**3.42**) for the Tricyclic Isocarbacyclin Analogues.

The resulting diester (**3.38**) was expected to act similarly in the mesylation as in the model system. Unfortunately, another unknown byproduct formed in addition to the desired mesylate (**3.39**). Different conditions were screened (Table 3.5) to form the mesylate (entries 1-6), bromide (entries 7, 8) or triflate (entries 9-11) derivatives that could work as a starting material for the next Stille coupling step. All trials either resulted in a byproduct along with the product in the case of the mesylate and the bromide or no reaction in the case of the triflate.

Table 3.5. Different Conditions for the Synthesis of Stille Coupling Starting Material in the Real System of the Tricyclic Analogues.[a]



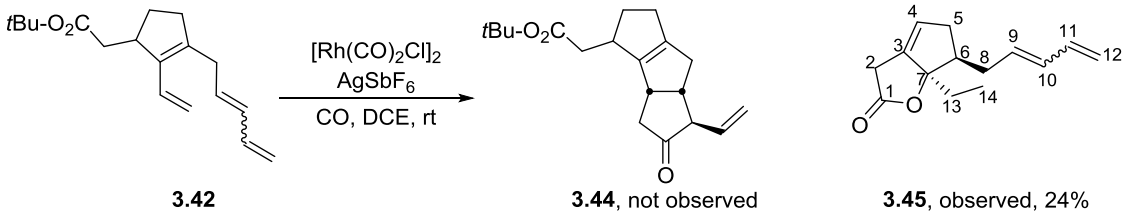
Entry	X	Reactant	Additive	Temp	Solvent	Time
1	OMs	MsCl (2.6 eq)	Et_3N (4.9 eq)	0 °C - rt	DME	overnight
2		MsCl (2.6 eq)	Et_3N (4.9 eq)	0 °C - rt	DME	4 hr
3		MsCl (6.6 eq)	Et_3N (6.9 eq)	-40 °C - rt	DME	overnight
4		MsCl (5.6 eq)	Et_3N (10.9 eq)	-20 °C - rt	DME	30 min
5		MsCl (7.6 eq)	Et_3N (14.9 eq)	0 °C - rt	THF	overnight
6		MsCl (2.6 eq)	NaH (1.5 eq)	0 °C - rt	THF	overnight
7	Br	oxalyl bromide (1.5 eq)	DMF (1.3 eq)	0 °C - rt	CH_2Cl_2	4 hr
8		oxalyl bromide (1.5 eq)	Et_3N (2.0 eq)	0 °C - rt	CH_2Cl_2	overnight
9	OTF	Comins' reagent (2.5 eq)	NaH (1.5 eq)	0 °C - rt	THF	4 hr
10		Comins' reagent (2.5 eq)	NaH (1.5 eq)	0 °C - rt	THF	overnight
11		Comins' reagent (1.4 eq)	LiHMDS (1.2 eq)	-78 °C - rt	THF	overnight

[a]Reactions Conditions: Diester (**3.38**, 1 eq), solvent (0.1 M).

At that point we decided to move forward although mesylate (**3.39**) was not fully characterized. The crude mesylate product was subjected to Pd^0 catalysis for a Stille

coupling in the same way as in the model system to generate dienoic ester **3.40** in a 20% yield over the two steps. Dienoic ester **3.40** was subjected to LiOH to hydrolyze selectively the methyl ester and afford dienoic acid (**3.41**) that reacts with bisallylic alcohol (**3.4**) to get the decarboxylated tetraene (**3.42**).

Tetraene (**3.42**) was expected to react in the next step as in the model system. However; it did not react when subjected to $[RhCl(CO)_2]_2$ under carbon monoxide atmosphere at 80 °C. On the other hand, reacting tetraene **3.42** with $[RhCl(CO)_2]_2$ catalyst at room temperature and $AgSbF_6$ as an additive resulted in a different reaction with an unknown mechanism and afforded structure **3.45** (Scheme 3.10). The molecular formula for the resulted structure (**3.45**) was determined to be $C_{14}H_{18}O_2$ by its HRESIMS, which required 6 degrees of unsaturation similar to tetraene **3.42**. The ^{1}H and ^{13}C NMR spectra of **3.45**, interpreted with the aid of COSY, HSQC and HMBC spectra, revealed the presence of one CH_3 [δ_H 0.86; δ_C 7.7], 5 CH_2 including one vinylic [δ_H 5.19; δ_C 118.2] and 4 aliphatic [δ_H 2.90, 2.63, 2.34, 2.14 and 1.85; δ_C 38.2, 38.1, 28.6 and 24.8], 5 CH including 4 vinylic [δ_H 6.59, 6.12 and 5.55 (2H); δ_C 131.8, 130.9, 128.4 and 128.1] and one aliphatic [δ_H 2.82 (dddd); δ_C 39.5] and 3 fully substituted carbons which are one carbonyl [δ_C 176.9], one vinylic [δ_C 142.3] and one aliphatic [δ_C 101.9]. Moreover ^{1}H and ^{13}C NMR spectra of **3.45** shows the formation of two *E* and *Z* isomers at C9-C10 double bond in a 4.0:1.0 ratio.



Scheme 3.10. Cyclization of Bis-Diene **3.42** to Afford the Unanticipated Bicycle **3.45**.

The COSY correlations of H_{13} and H_{14} suggests the presence of the ethyl group. Additionally, the chemical shifts and sequential COSY correlations of H_8, H_9, H_{10}, H_{11} and H_{12} suggests the presence of a pentadienyl chain. The HMBC correlations of H_{2a} and H_{2b}/C-1, H_{2a}, H_{2b}/C-7 explains the ring connections (Figure 3.3; **A**). The HMBC correlations of H_{13}, H_{14}/C-7 and H_{13}, H_{14}/C-3 suggests that the ethyl group is on a fully substituted carbon and explains the way the two rings are connected. The HMBC correlation of H_5/C-3 explains linking of a methylene to the C-3/C-4 double bond. The NOESY correlations of H_{13}/H_6 explains the stereochemistry of the two stereocenters C6/C7 (Figure 3.3; **B**).

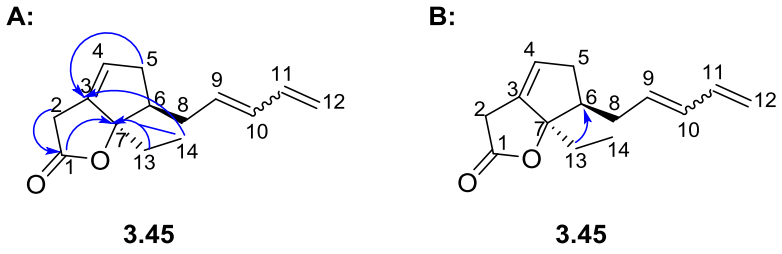


Figure 3.3. **A:** Selected Key HMBC Correlations of Structure **3.45**. **B:** Selected Key NOESY Correlations of Structure **3.45**.

3. Conclusion

In summary, we present an enantioselective synthesis of isocarbacyclin in 10 steps using three transition metal-catalyzed reactions including Pd^0-catalyzed decarboxylation, Rh^I-catalyzed cycloaddition and Ru^{II}-catalyzed cross-metathesis. This synthetic approach of isocarbacyclin takes advantage of attaching an ω-side chain at a late stage in the synthesis, which enabled us to synthesize other analogues from the same bicyclic building block by attaching different alkenyl ω-side chains. A limitation of this synthesis is the low yield of the cycloaddition step which led us to develop a new synthesis for tricyclic analogues to increase the yield of that step. A model synthesis worked successfully for this synthesis, however, efforts toward the cycloaddition step failed and resulted in a different type of reaction. Future efforts toward a tricyclic analogue will need to reveal the carboxyl group at a later stage.

4. Experimental and Characterization Data

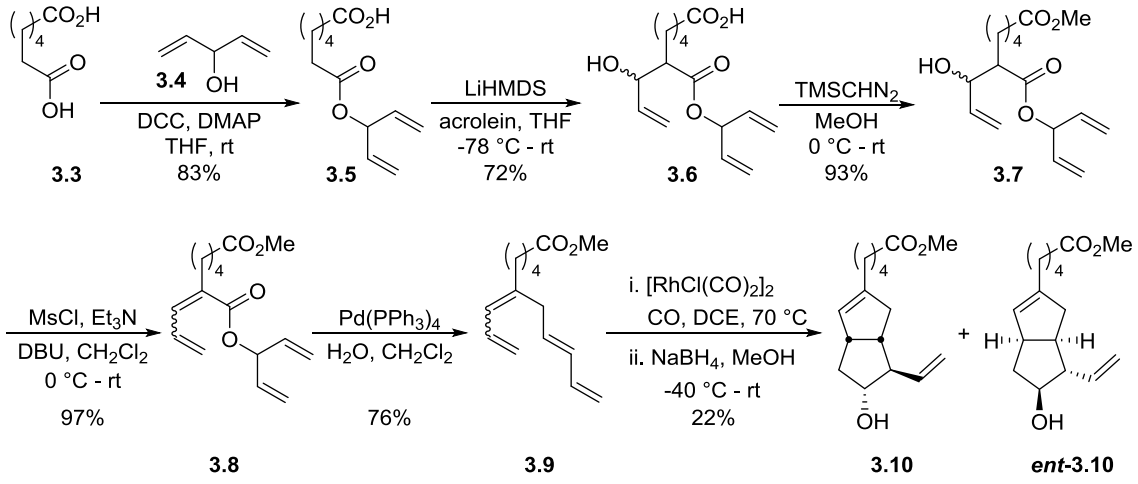
4.1 General Information

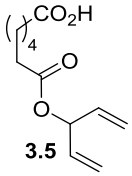
All anhydrous reactions were performed in oven dried glassware under a nitrogen atmosphere. Unless otherwise noted, all solvents and reagents were obtained from commercial sources and used without further purification. Tetrahydrofuran (THF) and dichloromethane (CH_2Cl_2) were obtained dry from the solvent system and degassed under a dry atmosphere of nitrogen. 1,2-dichloroethane (DCE), dimthoxyethane (DME), 2,2,2-trifluoroethanol (TFE) and methanol (MeOH) were obtained dry from Sigma Aldrich and degassed under a dry atmosphere of nitrogen or carbon monoxide.

Chromatographic purification was performed using silica gel (60 Å, 32-63 μm). NMR spectra were recorded in $CDCl_3$ using a JEOL ECA 400 spectrometer (400 MHz for 1H, 100 MHz for ^{13}C, and 376.5 MHz for ^{19}F), JEOL ECA spectrometer (500 MHz for ^{1}H and 125 MHz for ^{13}C) and an Agilent 700-NMR spectrometer equipped with a ^{1}H ($^{13}C/^{15}N$) 5 mm Enhanced Cold Probe (176 MHz for ^{13}C). Coupling constants, *J*, are reported in hertz (Hz) and multiplicities are listed as singlet (s), doublet (d), triplet (t), quartet (q), quintet (quint), doublet of doublets (dd), triplet of triplets (tt), multiplet (m), etc. High Resolution Mass Spectra were acquired on a Thermo Fisher Scientific LTQ Orbitrap XL MS system. Analytical GC data was collected with an Agilent 7890A gas chromatograph with BetaDex 110 Fused Silica Capillary Column (30 m x 0.25 mm with 0.25 μm film thickness). GC runs were performed with a flow rate of 3 mL/min, injection temperature of 250 °C, and an initial oven temperature of 40 °C for 60 minutes. The temperature was increased to 80 °C at a rate of 2 °C per minute, oven temperature was held at 80 °C for 10 minutes and finally the temperature was increased to 170 °C at a rate of 5 °C per minute and held at 170 °C for 5 minutes.

4.2 Synthesis of Isocarbacyclin and Analogues

4.2.1 Synthesis of the Bicyclic Core, 3.10



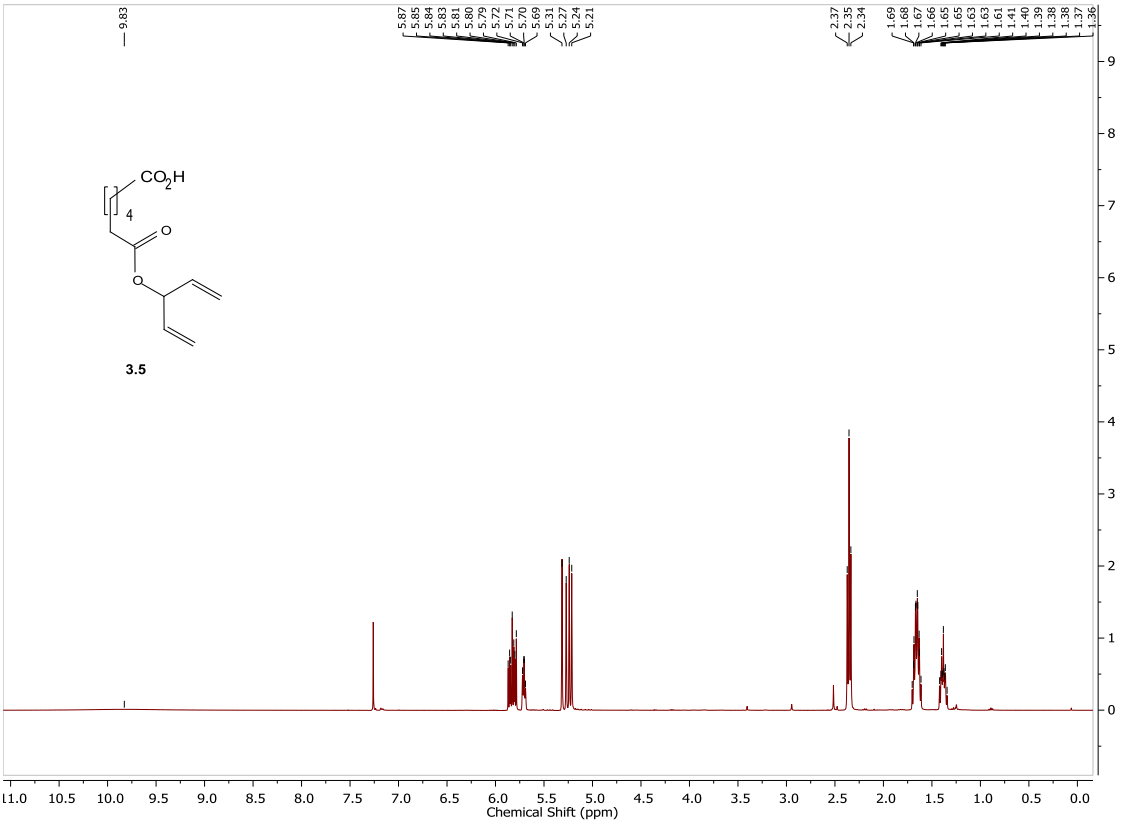


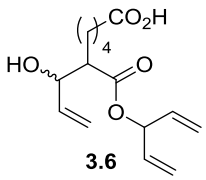
7-oxo-7-(penta-1,4-dien-3-yloxy)heptanoic acid, 3.5

A solution of DCC (2.5 g, 12 mmol) in THF (15 mL) was added to a solution of pimelic acid **3.3** (9.5 g, 59 mmol), 1,4-pentadien-3-ol **3.4** (1.2 mL, 12 mmol), and DMAP (145 mg, 1.2 mmol) in THF (90 mL) slowly via an additional funnel over 3 hours. After 48 hours, the reaction was filtered through Celite® and washed with THF. Silica gel was added to the concentrated mixture and the solvent was removed after which the dry powder was added to a silica gel column. The product was purified (70:30, hexanes/

EtOAc) to yield acid **3.5** (2.1 g, 83%) as colorless oil. R_f = 0.23 (70:30, hexanes/ EtOAc). The NMR spectra matched previous reported data.[20]

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.83 (bs, 1H), 5.83 (ddd, *J* = 16.9, 10.4, 6.0 Hz, 2H), 5.72 – 5.69 (m, 1H), 5.31 – 5.21 (m, 4H), 2.35 (t, *J* = 7.5 Hz, 4H), 1.69 – 1.61 (m, 4H), 1.41 – 1.36 (m, 2H) ppm.





7-hydroxy-6-((penta-1,4-dien-3-yloxy)carbonyl)non-8-enoic acid, 3.6

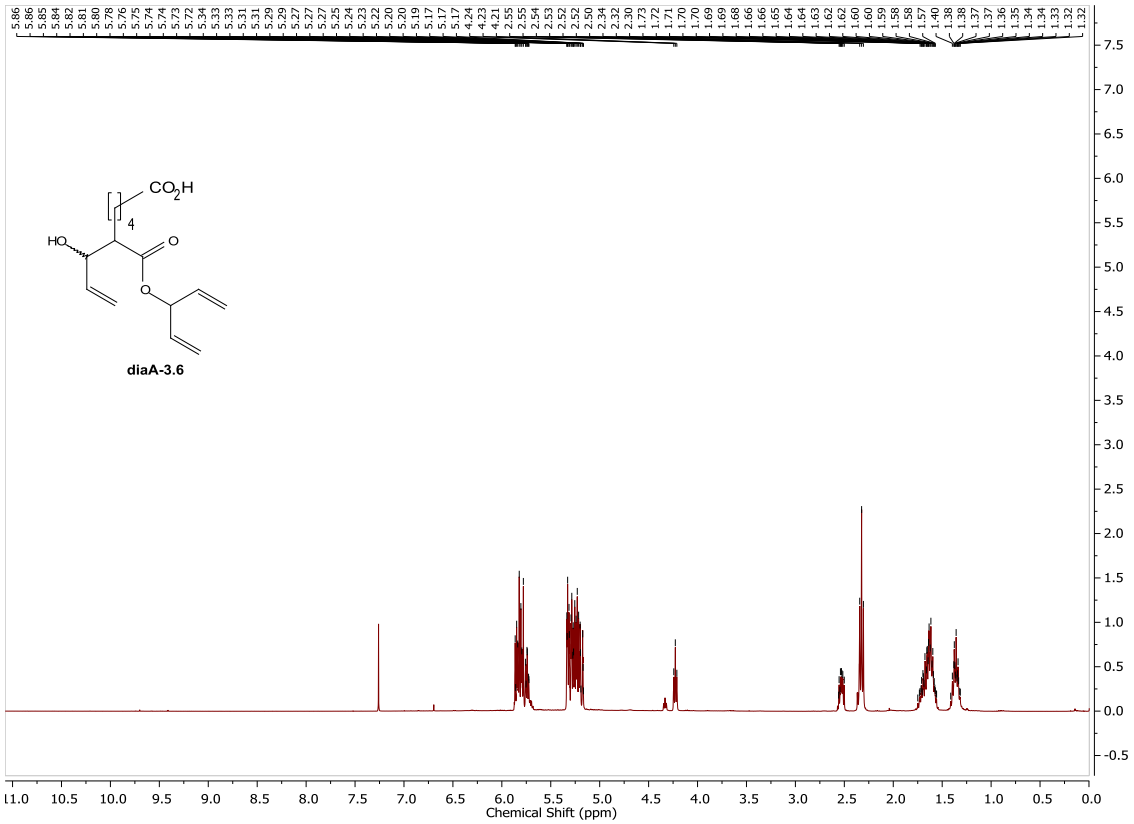
To a solution of LiHMDS (2.2 g, 13 mmol) in THF (12 mL) at -78 °C was slowly added acid **3.5** (1.0 g, 4.4 mmol) in THF (6 mL). After stirring for 15 minutes, the reaction was transferred via a cannula quickly to a mixture of acrolein (2.9 mL, 44 mmol) in THF (22 mL) cooled to -78 °C. Additional THF (4 mL) was transferred as a wash and the mixture was warmed to room temperature for 15 minutes. The reaction was quenched by addition of saturated NH_4Cl solution (10 mL). After 2 extractions with EtOAc, a 10% aqueous HCl was added to the aqueous layer until pH ~ 3. This addition was followed by 2 more extractions with EtOAc. The combined organic layers were dried using Na_2SO_4 and filtered. The organic layers were then concentrated and purified via silica gel chromatography (65:35, hexanes/EtOAc) which yielded alcohol **3.6** (0.87 g, 70%) as a brown oil. Two isomers are produced, diastereomer A and B. The diastereomeric ratio is 1:1 with diastereomer A eluting early. The NMR spectra matched previous reported data.[20]

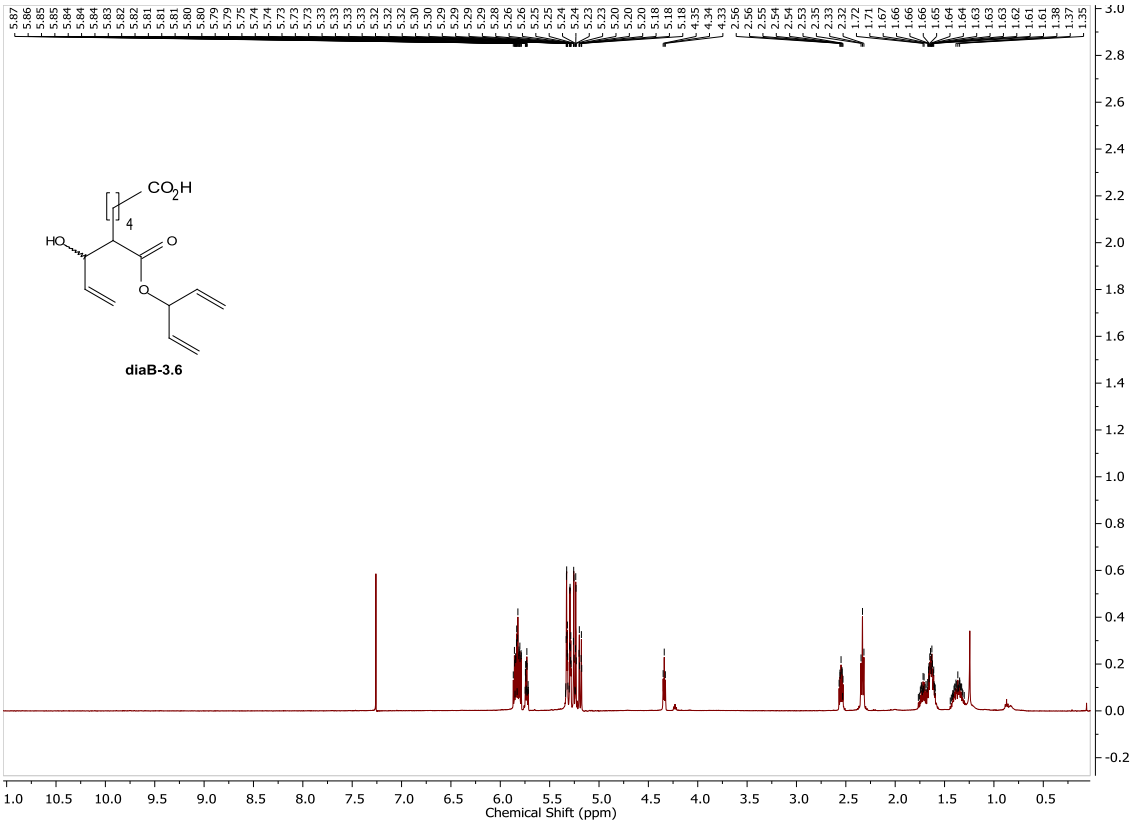
Diastereomer A:

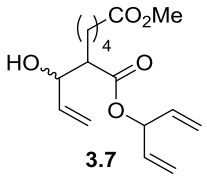
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.86 – 5.78 (m, 3H), 5.76 – 5.72 (m, 1H), 5.34 – 5.17 (m, 6H), 4.23 (t, J = 6.3 Hz, 1H), 2.56 – 2.50 (m, 1H), 2.32 (t, J = 7.5 Hz, 2H), 1.75 – 1.56 (m, 4H), 1.41 – 1.32 (m, 2H) ppm. R_f = 0.67 (50:50, hexanes/EtOAc).

Diastereomer B:

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.87 – 5.79 (m, 3H), 5.72 – 5.75 (m, 1H), 5.34 – 5.18 (m, 6H), 4.34 (t, J = 5.6 Hz, 1H), 2.57 – 2.53 (m, 1H), 2.33 (t, J = 7.3, 2H), 1.77 – 1.59 (m, 4H), 1.44 – 1.30 (m, 2H) ppm. R_f = 0.57 (50:50, hexanes/EtOAc).


CO2H
4
HO
O
O
diaA-3.6
Chemical Shift (ppm)





7-methyl 1-penta-1,4-dien-3-yl 2-(1-hydroxyallyl)heptanedioate, 3.7

To a solution of alcohol **3.6** (705 mg, 2.5 mmol) in MeOH (25 mL) that was cooled to 0 °C was slowly added a 2M solution of trimethylsilyldiazomethane in diethyl ether (6.9 mL, 14 mmol). After 15 minutes of stirring, N_2 was bubbled through the reaction for 20 minutes and the reaction was concentrated before purification via silica gel chromatography (80:20, hexanes/EtOAc). Purification yielded ester **3.7** (688 mg,

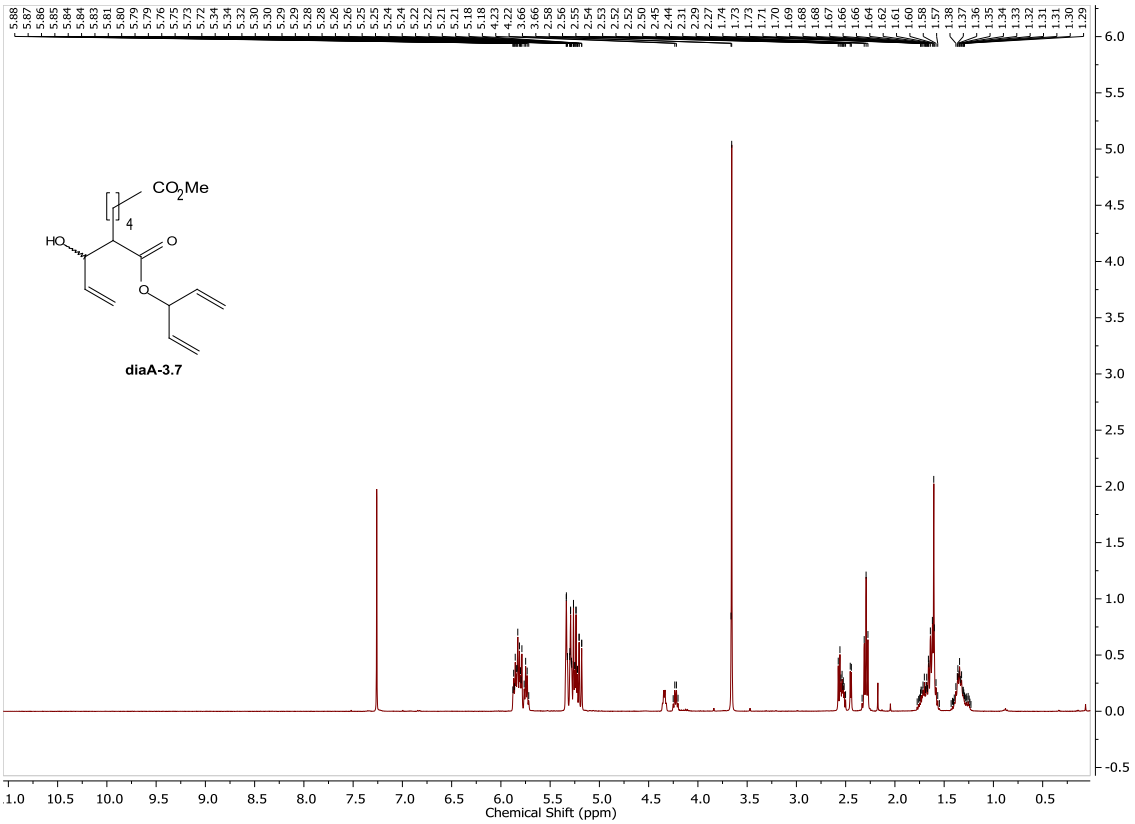
93%) as a yellow oil. Two isomers are produced, diastereomer A and B. The diastereomeric ratio is 1:1 with diastereomer A eluting early. The NMR spectra matched previous reported data.[20]

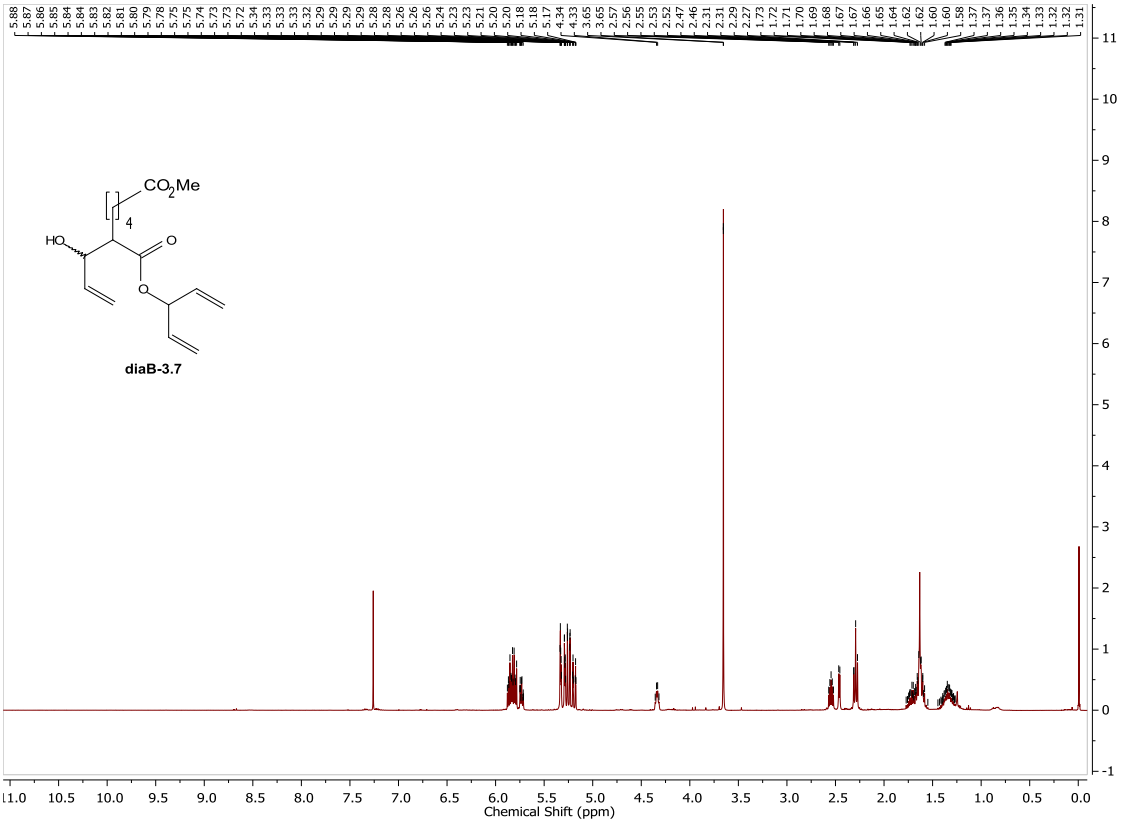
Diastereomer A:

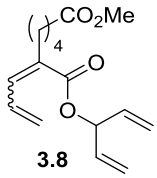
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.88 – 5.79 (m, 3H), 5.76 – 5.72 (m, 1H), 5.34 – 5.26 (m, 3H), 5.25 – 5.22 (m, 2H), 5.21 – 5.18 (m, 1H), 4.23 (q, J = 6.4 Hz, 1H), 3.66 (s, 3H), 2.58 – 2.50 (m, 1H), 2.45 (d, J = 4.5 Hz, OH), 2.31 – 2.27 (m, 2H), 1.77 – 1.55 (m, 4H), 1.43 – 1.24 (m, 2H) ppm. R_f = 0.41 (80:20, hexanes/EtOAc).

Diastereomer B:

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.88 – 5.78 (m, 3H), 5.75 – 5.71 (m, 1H), 5.34 – 5.28 (m, 3H), 5.26 – 5.23 (m, 2H), 5.19 (dt, J_d = 10.5, J_t = 1.4 Hz, 1H), 4.34 (q, J_q = 5.4 Hz, 1H), 3.65 (s, 3H), 2.55 (quint, J = 4.0 Hz, 1H), 2.46 (d, J = 4.5 Hz, 1H, OH), 2.31 – 2.27 (m, 2H), 1.77 – 1.55 (m, 4H), 1.44 – 1.27 (m, 2H) ppm. R_f = 0.31 (80:20, hexanes/EtOAc).


CO2Me
4
HO
O
O
diaA-3.7
Chemical Shift (ppm)





(*E*/*Z*)-7-methyl 1-penta-1,4-dien-3-yl 2-allylideneheptanedioate, 3.8

To a solution of ester **3.7** (600 mg, 2.0 mmol) and triethylamine (1.1 mL, 8.1 mmol) in CH_2Cl_2 (20 mL) that was cooled to 0 °C was slowly added methane sulfonyl chloride (0.47 mL, 6.0 mmol). After 10 minutes, 1,8-diaza\bicycloundec-7-ene (2.0 mL, 13 mmol) was added and the reaction was allowed to warm to room temperature. After an additional hour, more 1,8-diazobicycloundec-7-ene (2.0 mL, 13 mmol) was added. The

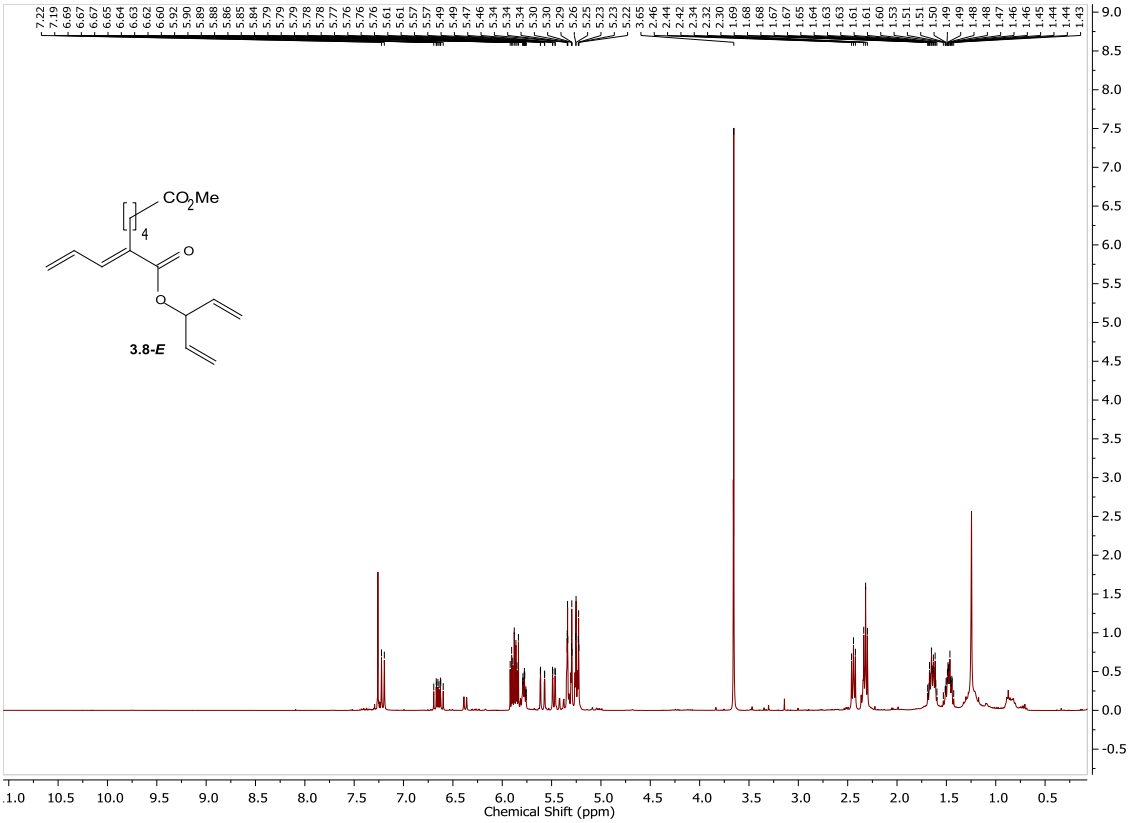
reaction was stirred for another 18 hours after which the reaction was poured over saturated $NaHCO_3$ solution and the product was extracted 3x with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated before being purified via silica gel chromatography (90:10, hexanes/EtOAc) to yield diene **3.8** (548 mg, 97%) as a colorless oil. The NMR spectra matched previous reported data.[20]

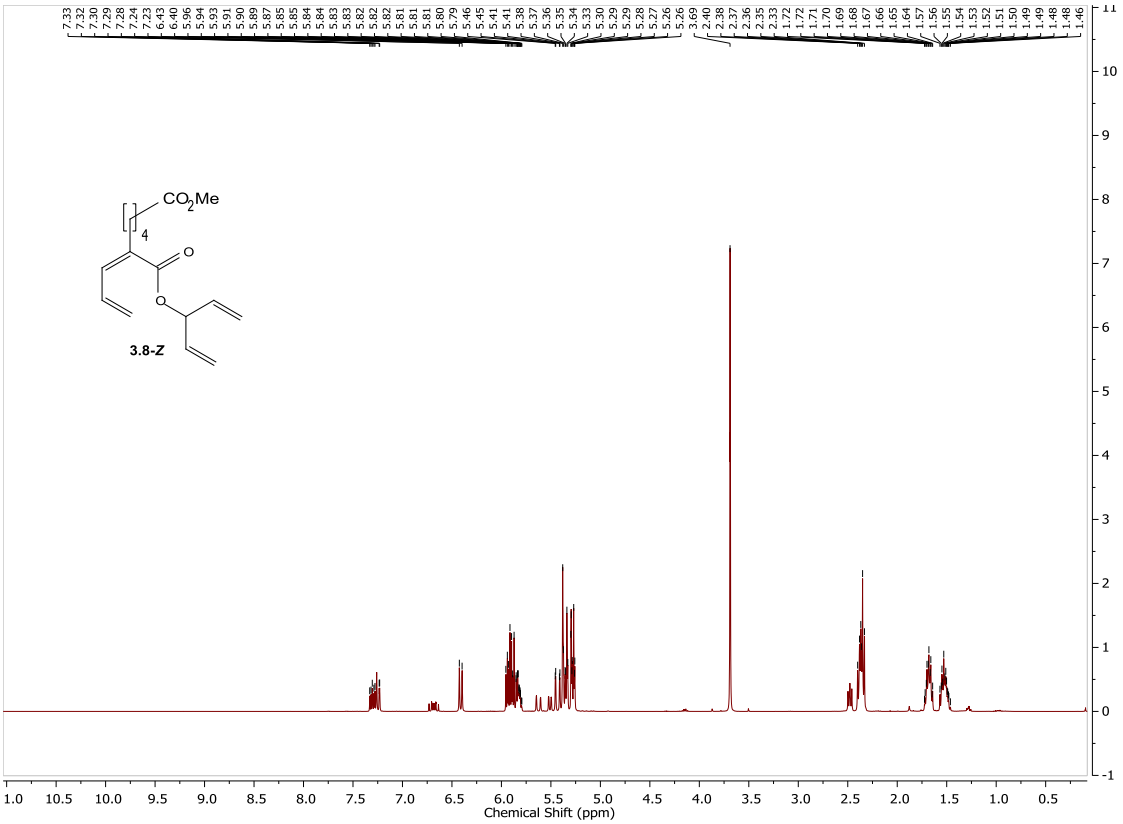
E Diastereomer:

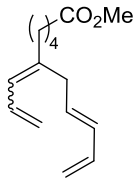
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, *J* = 11.4 Hz, 1H), 6.65 (ddd, *J* = 16.8, 11.4, 10.0 Hz, 1H), 5.88 (ddd, *J* = 16.9, 10.4, 5.9 Hz, 2H), 5.78 (tt, *J* = 5.8, 1.0 Hz, 1H), 5.59 (dd, *J* = 16.8, 1.7 Hz, 1H), 5.47 (dd, *J* = 10.3, 1.7 Hz, 1H), 5.31 (dt, J_d = 17.2, J_t = 1.4 Hz Hz, 2H), 5.24 (dt, J_d = 10.0, J_t = 1.3 Hz, 2H), 3.65 (s, 3H), 2.44 (t, *J* = 7.6, 2H), 2.32 (t, *J* = 7.4, 2H), 1.69 – 1.60 (m, 2H), 1.53 – 1.43 (m, 2H) ppm. R_f = 0.78 (70:30, hexanes/EtOAc).

Z Diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.23 (m, 1H), 6.41 (d, *J* = 11.1 Hz, 1H), 5.91 (ddd, *J* = 16.6, 10.3, 5.9 Hz, 2H), 5.85 – 5.79 (m, 1H), 5.43 (dd, *J* = 17.0, 1.9 Hz, 1H), 5.38 – 5.33 (m, 3H), 5.30 – 5.26 (m, 2H), 3.69 (s, 3H), 2.40 – 2.33 (m, 4H), 1.72 – 1.64 (m, 2H), 1.57– 1.46 (m, 2H) ppm. R_f = 0.71 (70:30, hexanes/EtOAc).


CO2Me
4
O
O
3.8-E
Chemical Shift (ppm)





3.9

(6*E*/*Z*,8*E*)-methyl 6-allylideneundeca-8,10-dienoate, 3.9

To a microwave vial was added ester **3.8** (40 mg, 0.14 mmol) and water (2.7 µL, 0.15 mmol) in CH_2Cl_2 (2 mL). Tetrakis-(triphenylphosphine) palladium (16 mg, 0.014 mmol) was added and the vial was sealed and purged with N_2. The mixture was a bright orange color. After 24 hours at room temperature, the mixture was a turbid yellow color. The reaction was concentrated and purified via silica gel chromatography (97:3,

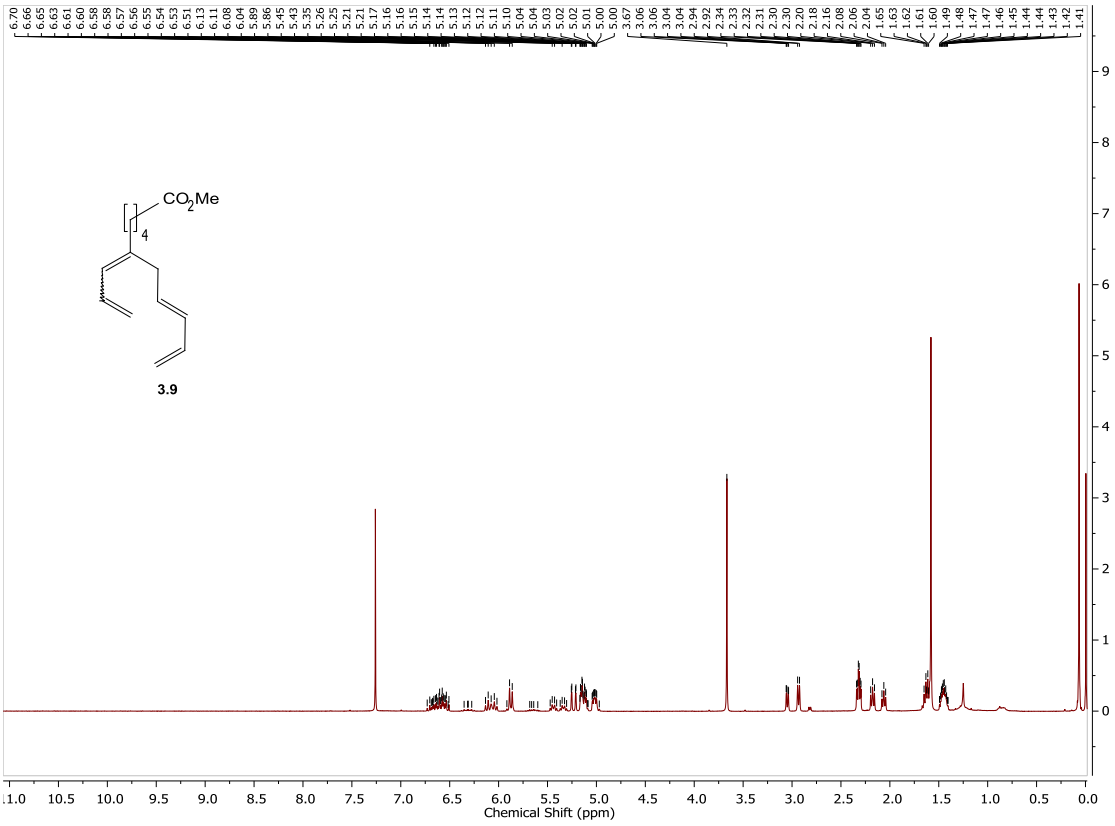
hexanes/EtOAc) to yield tetraene **3.9** (22 mg, 76%) as a light yellow oil. Scale-up beyond 100 mg resulted in decreased yields; however, when eight vials were run simultaneously and purified together, the yield remained around 70%. The NMR spectra matched previous reported data.[20]

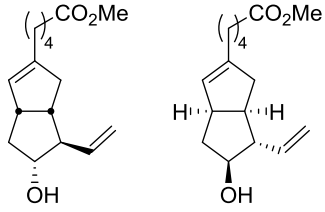
E Diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.73 – 6.51 (m, 2H), 6.08 (t, *J* = 10.9 Hz, 1H), 5.87 (d, *J* = 11.0 Hz, 1H), 5.44 (q, *J* = 8.2 Hz, 1H), 5.23 (dd, *J* = 16.9, 1.9 Hz, 1H), 5.16 – 5.10 (m, 2H), 5.04 – 5.00 (m, 1H), 3.67 (s, 3H), 2.93 (d, *J* = 7.7 Hz, 2H), 2.32 (td, J_t = 7.5, J_d = 3.3 Hz, 2H), 2.18 (t, *J* = 7.8 Hz, 2H), 1.67 – 1.59 (m, 2H), 1.49 – 1.40 (m, 2H) ppm. R_f = 0.56 (90:10, hexanes/EtOAc).

Z Diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.73 – 6.51 (m, 2H), 6.05 (t, *J* = 10.9 Hz, 1H), 5.87 (d, *J* = 10.9 Hz, 1H), 5.34 (q, *J* = 7.5 Hz, 1H), 5.23 (dd, *J* = 16.9, 1.4 Hz, 1H), 5.17 – 5.09 (m, 2H), 5.04 – 5.00 (m, 1H), 3.67 (s, 3H), 3.06 (d, *J* = 7.6 Hz, 2H), 2.34 – 2.30 (m, 2H), 2.06 (t, *J* = 7.4 Hz, 2H), 1.67 – 1.59 (m, 2H), 1.49 – 1.40 (m, 2H) ppm. R_f = 0.50 (90:10, hexanes/EtOAc).





3.10

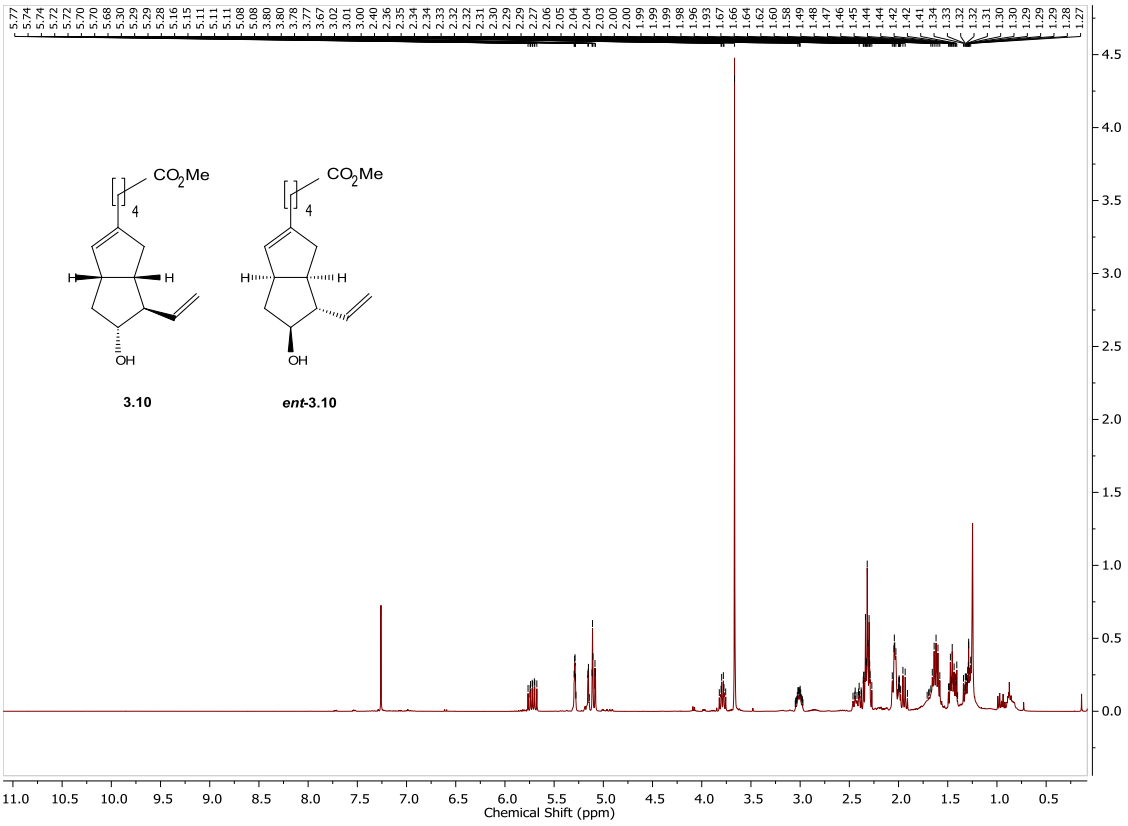
***ent*-3.10**

Bicycle, 3.10

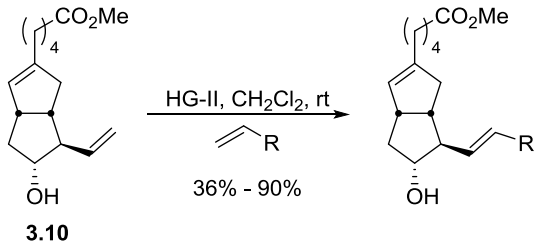
To a solution of tetraene **3.9** (19 mg, 0.09 mmol) in 1,2-dichloroethane (1.2 mL) was added $[RhCl(CO)_2]_2$ (3.5 mg, 0.009 mmol) before purging thoroughly with CO. A CO filled balloon was used to maintain a constant CO atmosphere and the reaction was heated to 70 °C using an oil bath for 9 hours. The reaction was then cooled to -40 °C and

MeOH (0.9 mL) and triphenylphosphine (2.2 mg, 0.009 mmol) were added prior to the addition of $NaBH_4$ (6.4 mg, 0.17 mmol). After 20 minutes, the reaction was poured over water and extracted 2x with CH_2Cl_2. The aqueous layer was then acidified to a pH ~ 3 with 10% aqueous HCl after which two more extractions were done using CH_2Cl_2. The combined organic layers were then washed with brine, dried using Na_2SO_4 and finally concentrated. Purification via silica gel chromatography (90:10, hexanes/EtOAc) yielded bicycle **3.10** (4.6 mg, 22%) as a colorless oil. R_f = 0.38 (80:20, hexanes/EtOAc). The NMR spectra matched previous reported data.[20]

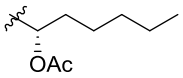
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.71 (ddd, J = 17.0, 10.1, 8.4 Hz, 1H), 5.30 – 5.28 (m, 1H), 5.18 – 5.03 (m, 2H), 3.78 (dt, J_d = 9.4, J_t = 7.1 Hz, 1H), 3.65 (s, 3H), 3.05 – 2.97 (m, 1H), 2.48 – 2.38 (m, 1H), 2.36 – 2.27 (m, 4H), 2.06 – 2.00 (m, 3H), 2.00 – 1.91 (m, 1H), 1.71 – 1.58 (m, 2H), 1.49 – 1.40 (m, 2H), 1.34 – 1.27 (m, 1H) ppm.

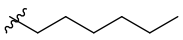


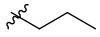
4.2.2 General Procedure A for Cross Metathesis of Isocarbacyclin and Derivatives, 3.14, 3.46 – 3.49

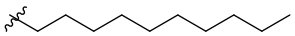


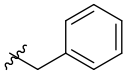
3.10

3.14, R = 

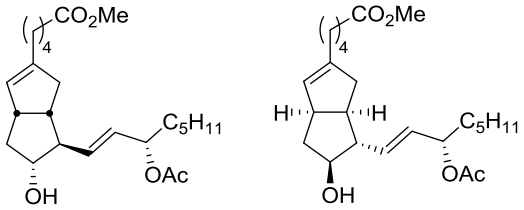
3.46, R = 

3.47, R = 

3.48, R = 

3.49, R = 

In a glove box, Hoveyda-Grubbs II catalyst (10 mol %) was quickly added to a microwave vial. The vial was sealed prior to removal from the glove box. To another vial, bicycle **3.10** (1 eq) and alkene (20 eq) were added and the vial was sealed, purged with N_2 and dissolved in degassed CH_2Cl_2 (0.1 M). The catalyst was dissolved in 0.1 mL of CH_2Cl_2 and added to the mixture. The reaction was covered with foil and left stirring at room temperature overnight. The mixture was concentrated and purified via silica gel chromatography to afford the cross metathesis products.



3.14 **dia-3.14**

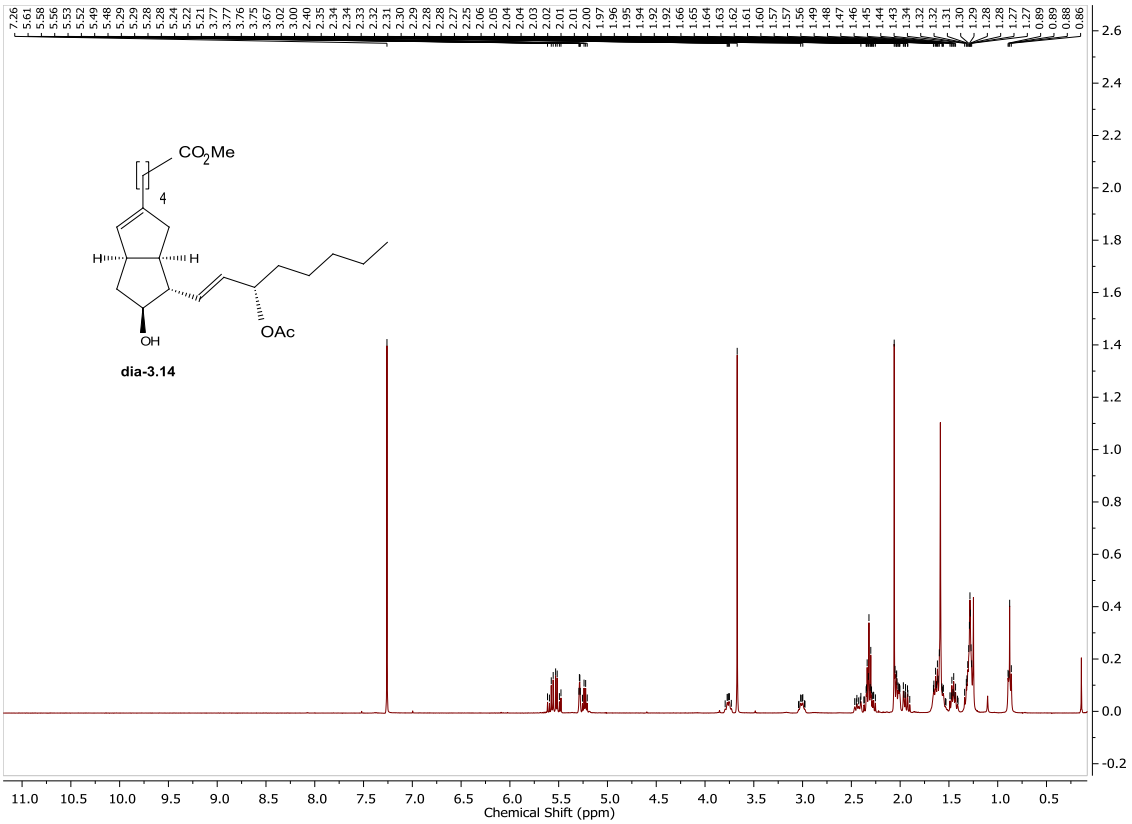
(15*S*)-acetoxy bicycle, 3.45 and dia-3.14

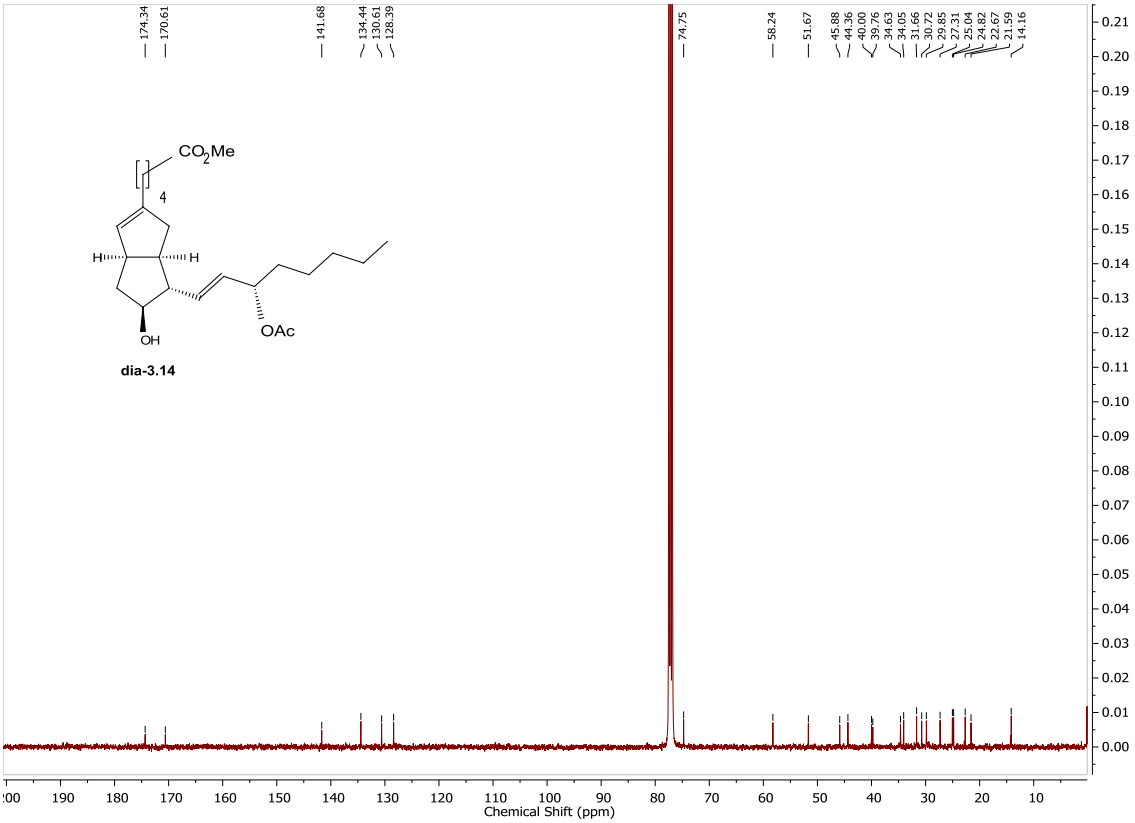
The crude product was purified via silica gel chromatography (85:15, hexanes/EtOAc) yielded two diastereomers separately, **3.14** and **dia-3.14**. The diastereomeric ratio is 1:1 with diastereomer **dia-3.14** eluting early.

Diastereomer **dia-3.14**: Colorless oil (3.00 mg, 20%), R_f = 0.35 (75:25, hexanes/EtOAc). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.61 – 5.48 (m, 2H), 5.29 – 5.28 (m, 1H), 5.26 – 5.21 (m, 1H), 3.76 (dt, J_d = 10.9 Hz, J_t = 7.9 Hz, 1H), 3.67 (s, 3H), 3.04 – 2.98 (m, 1H), 2.47 – 2.40 (m, 1H), 2.37 – 2.25 (m, 4H), 2.06 – 2.00 (m, 6H), 1.97 – 1.90 (m, 1H), 1.66 – 1.53 (m, 4H), 1.49 – 1.41 (m, 2H), 1.34 – 1.27 (m, 7H), 0.89 – 0.86 (m, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 174.3, 170.6, 141.7, 134.4, 130.6, 128.4, 74.8, 58.2, 51.7, 45.9, 44.4, 40.0, 39.8, 34.6, 34.1, 31.7, 30.7, 29.9, 27.3, 25.0, 24.8, 22.7, 21.6, 14.2 ppm.

HRMS (ESI) calcd. for $[C_{24}H_{38}O_5+H-C_2H_4O_2-H_2O]^+$: 329.2481, found: 329.2472.



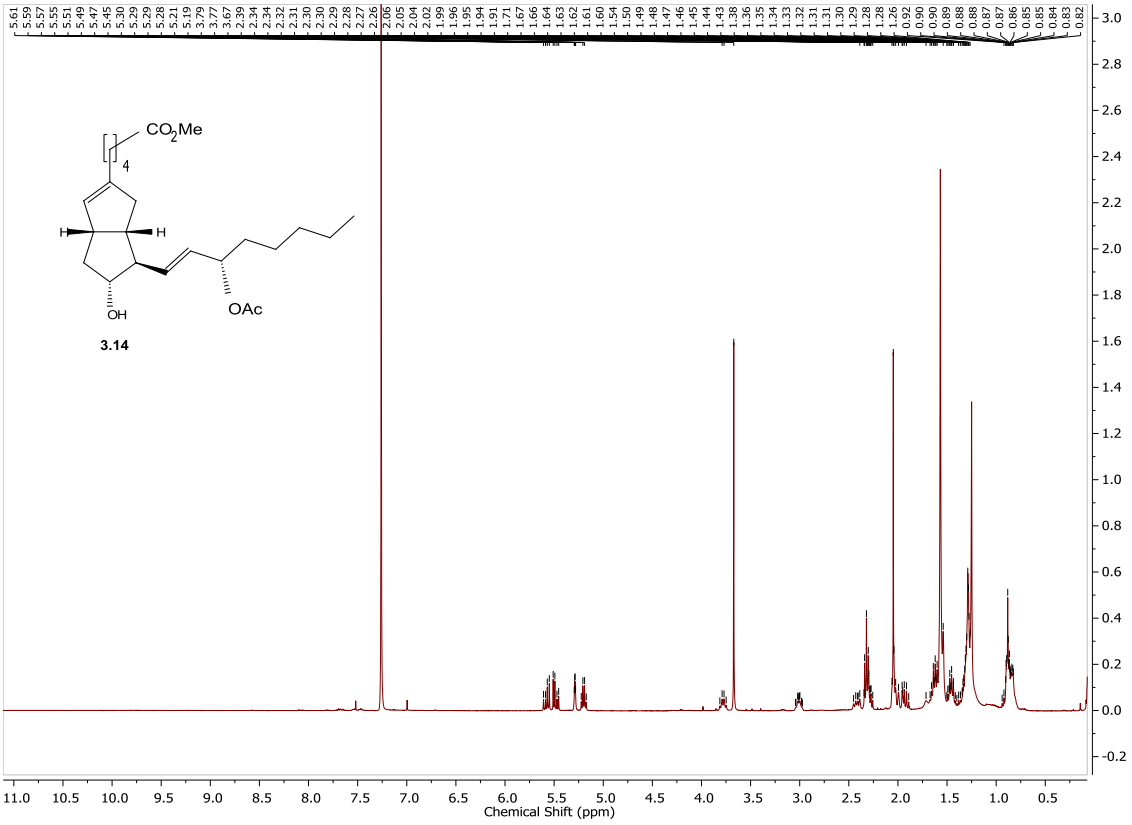


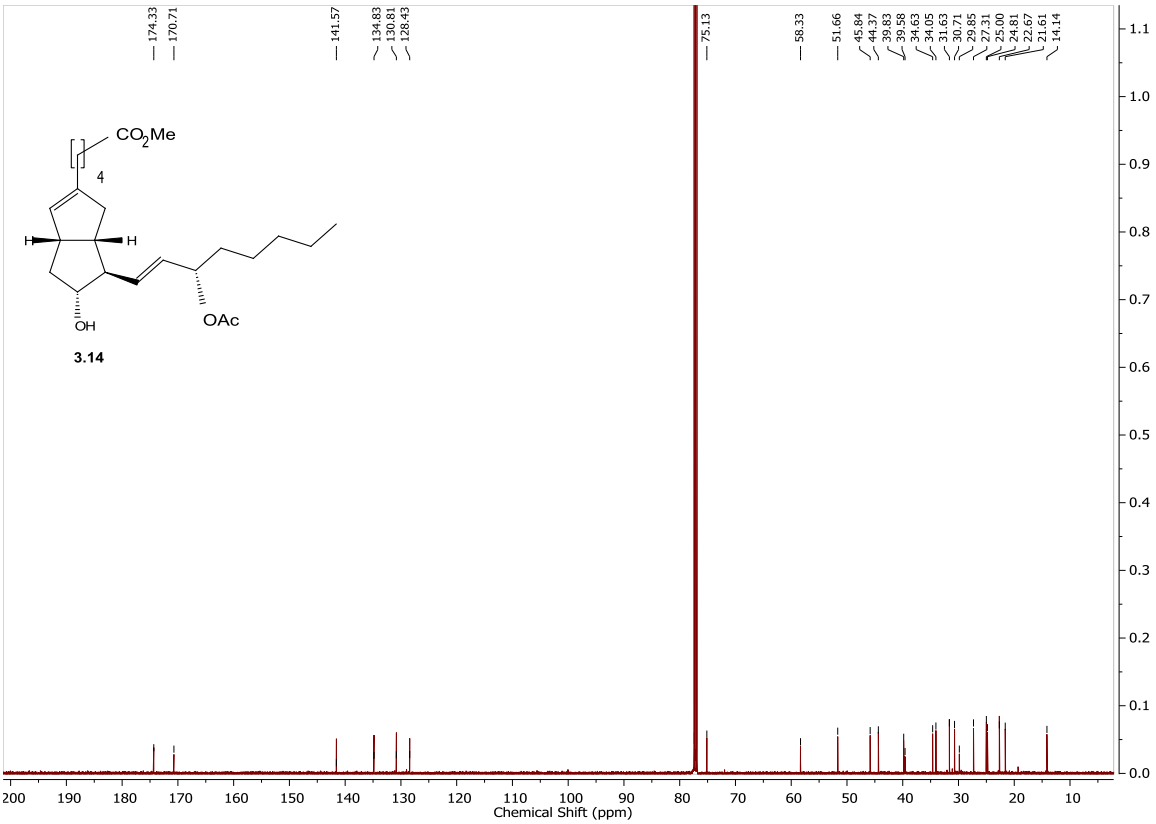
Diastereomer **3.14**: Colorless oil, (2.80 mg, 19%), R_f = 0.25 (75:25, hexanes/EtOAc).

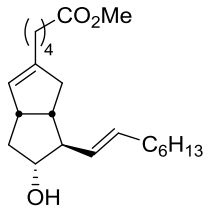
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.61 – 5.45 (m, 2H), 5.30 – 5.28 (m, 1H), 5.22 – 5.17 (m, 1H), 3.78 (q, *J* = 8.8 Hz, 1H), 3.67 (s, 3H), 3.04 – 2.97 (m, 1H), 2.45 – 2.39 (m, 1H), 2.34 – 2.26 (m, 4H), 2.06 – 1.99 (m, 5H), 1.96 – 1.89 (m, 2H), 1.71 – 1.54 (m, 4H), 1.50 – 1.40 (m, 2H), 1.38 – 1.26 (m, 7H), 0.94 – 0.82 (m, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$) δ 174.3, 170.7, 141.6, 134.8, 130.8, 128.4, 75.1, 58.3, 51.7, 45.8, 44.4, 39.8, 39.6, 34.6, 34.1, 31.6, 30.7, 29.9, 27.3, 25.0, 24.8, 22.7, 21.6, 14.1 ppm.

HRMS (ESI) calcd. for $[C_{24}H_{38}O_5+H-C_2H_4O_2-H_2O]^+$: 329.2481, found: 329.2472.







3.46

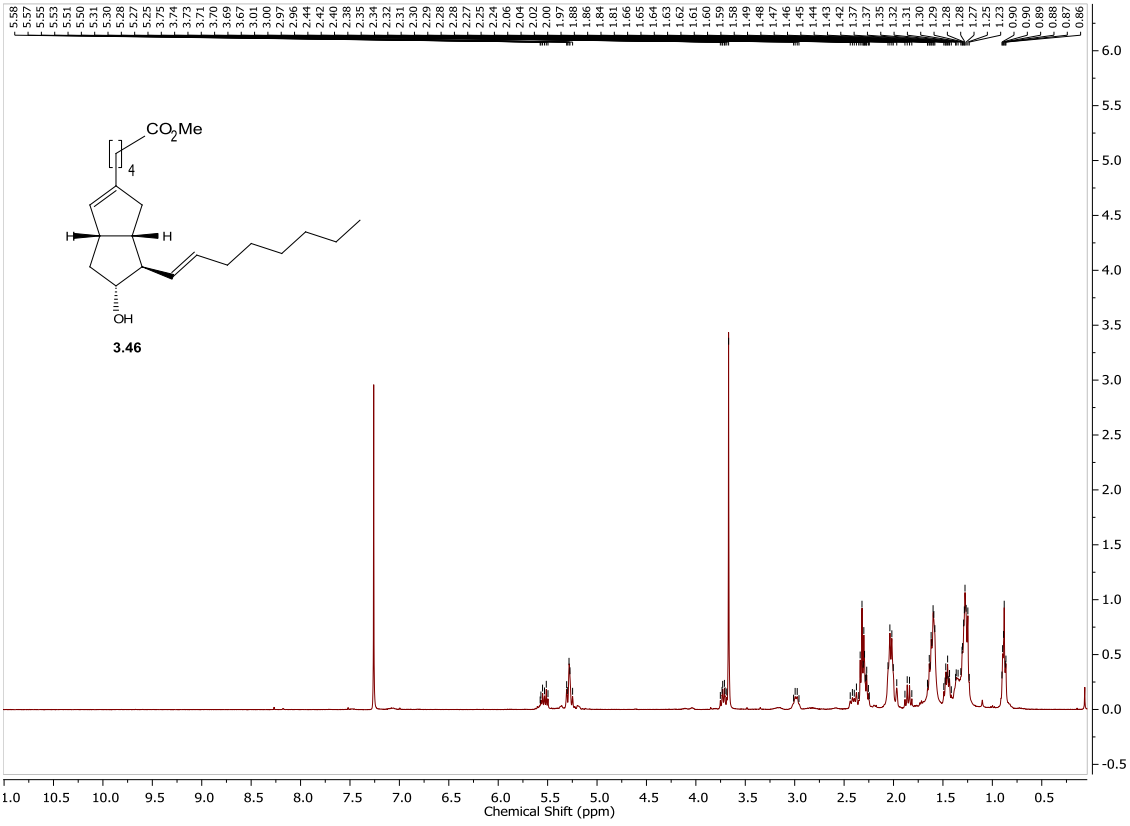
Methyl 2-((3a*S*,5*R*,6*R*,6a*S*)-5-hydroxy-6-((*E*)-oct-1-en-1-yl)-1,3a,4,5,6,6a-hexahydropentalen-2-yl)acetate, 3.46

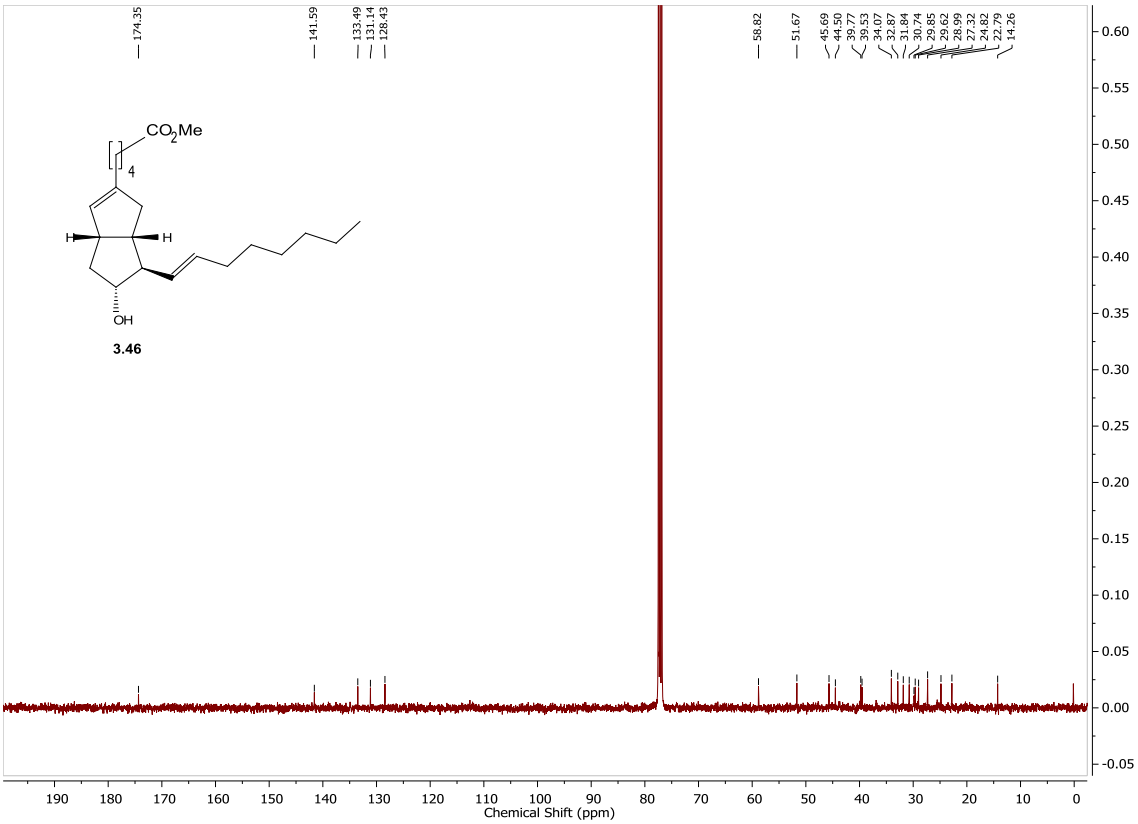
The crude product was purified via silica gel chromatography (90:10, hexanes/EtOAc) to yield ester **3.46** (5.0 mg, 90%) as a colorless oil. R_f = 0.38 (80:20, hexanes/EtOAc).

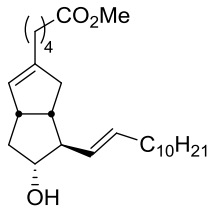
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.53 (dt, J_d = 14.1, J_t = 6.7 Hz, 1H), 5.31 – 5.25 (m, 2H), 3.72 (dt, J_d = 9.5, J_t = 6.9 Hz, 1H), 3.67 (s, 3H), 3.01 – 2.96 (m, 1H), 2.35 – 2.44 (m, 1H), 2.32 – 2.24 (m, 4H), 2.06 – 1.97 (m, 4H), 1.85 (q, J = 9.3 Hz, 1H), 1.66 – 1.58 (m, 6H), 1.49 – 1.42 (m, 2H), 1.37 – 1.23 (m, 6H), 0.90 – 0.86 (m, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4, 141.6, 133.5, 131.1, 128.4, 58.8, 51.7, 45.7, 44.5, 39.8, 39.5, 34.1, 32.9, 31.8, 30.7, 29.9, 29.6, 29.0, 27.3, 24.8, 22.8, 14.3 ppm.

HRMS (ESI) calcd. for $[C_{22}H_{36}O_3+H]^+$: 349.2737, found: 349.2726.







3.48

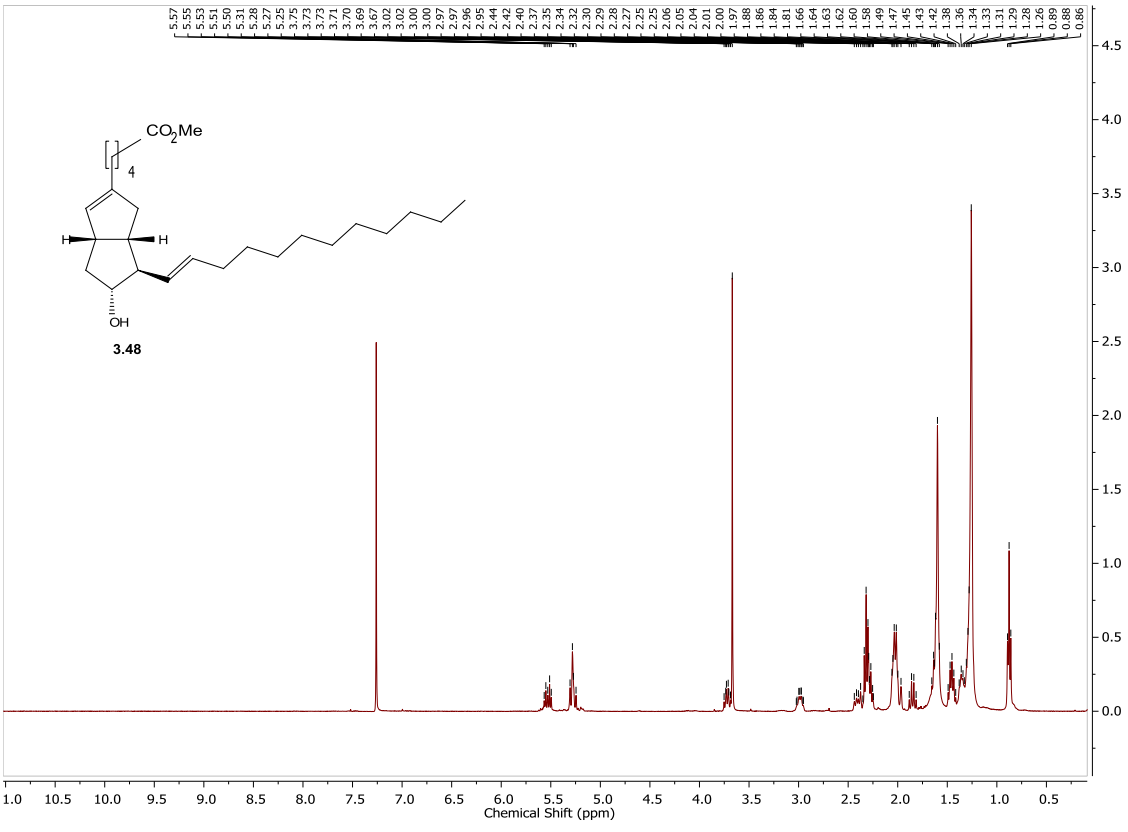
Methyl 2-((3a*S*,6*R*,6*R*,6a*S*)-6-((*E*)-dodec-1-en-1-yl)-5-hydroxy-1,3a,4,5,6,6a-hexahydropentalen-2-yl)actate, 3.48

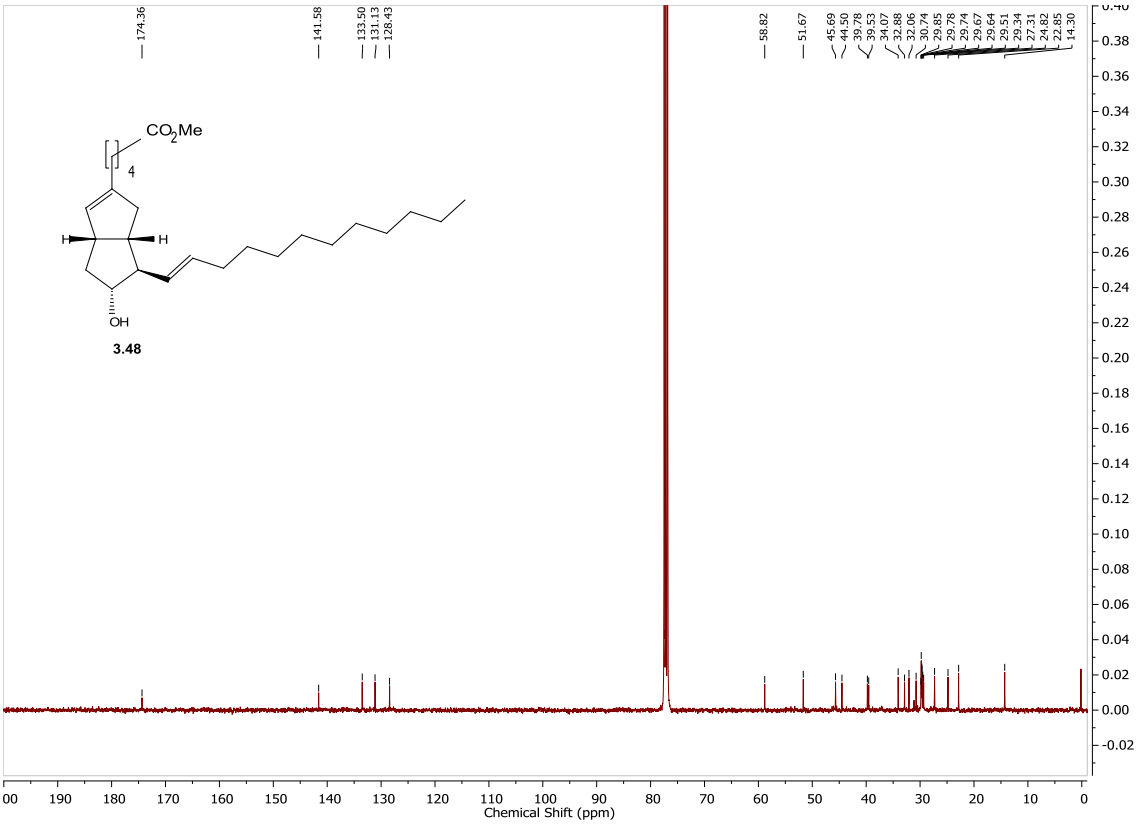
The crude product was purified via silica gel chromatography (92:8, hexanes/EtOAc) to yield ester **3.48** (3.3 mg, 60%) as a yellow oil. R_f = 0.61 (80:20, hexanes/EtOAc).

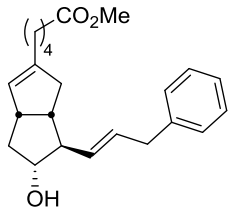
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.53 (dt, J_d = 14.1, J_t = 6.7 Hz, 1H), 5.31 – 5.25 (m, 2H), 3.72 (dt, J_d = 9.4, J_t = 6.7 Hz, 1H), 3.67 (s, 3H), 3.02 – 2.95 (m, 1H), 2.44 – 2.37 (m, 1H), 2.35 – 2.25 (m, 4H), 2.06 – 1.97 (m, 5H), 1.85 (q, J = 9.2 Hz, 1H), 1.66 – 1.58 (m, 2H), 1.45 (quint, J = 7.7 Hz, 2H), 1.38 – 1.26 (m, 18H), 0.88 (t, J = 6.6 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 174.2, 141.4, 133.4, 131.0, 128.3, 58.7, 51.5, 45.5, 44.4, 39.6, 39.9, 33.9, 32.7, 31.9, 30.6, 29.9, 29.7, 29.6, 29.5, 29.5, 29.4, 29.2, 27.2, 24.7, 22.7, 14.2 ppm.

HRMS (ESI) calcd. for $[C_{26}H_{45}O_3+H]^+$: 405.3363, found: 405.3357.







3.49

Methyl 2-((3a*S*,5*R*,6*R*,6a*S*)-5-hydroxy-6-((*E*)-3-phenylprop-1-en-1-yl)-1,3a,4,5,6,6a-hexahydropentalen-2-yl)acetate, 3.49

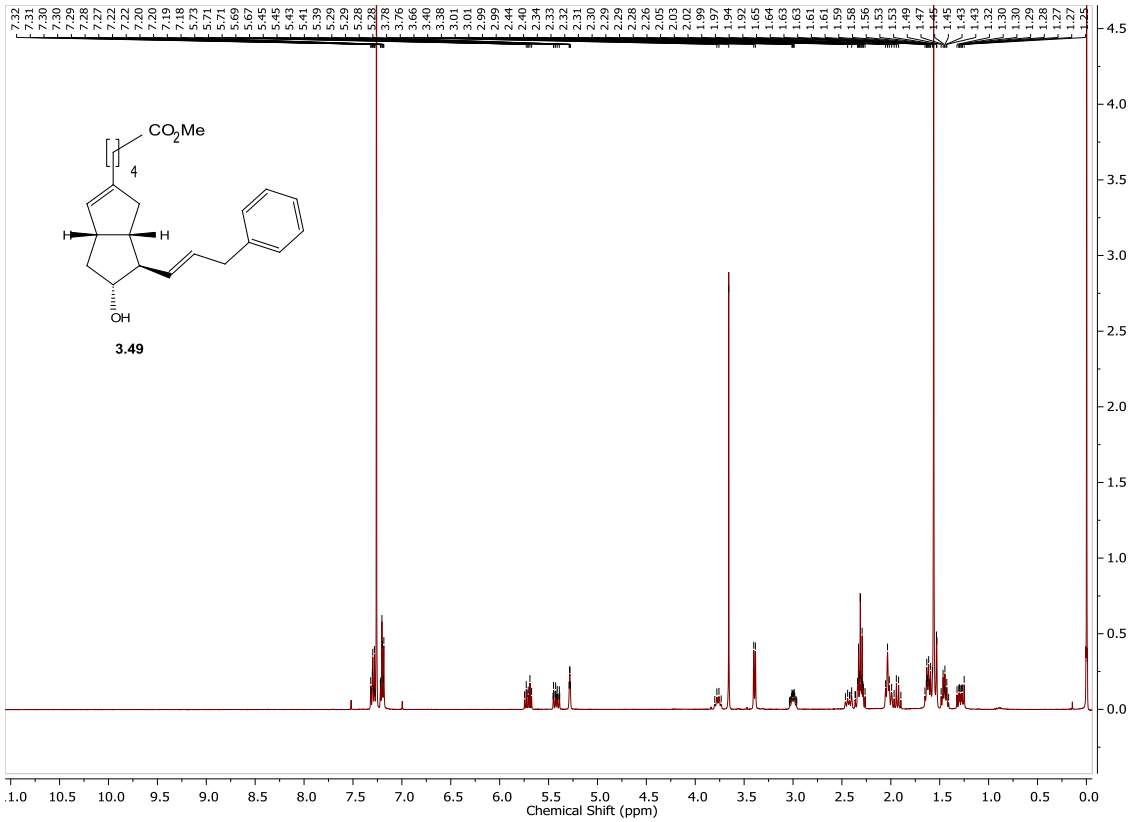
The crude product was purified via semi-preparative HPLC using a reverse phase C18 column (Gemini NX Gemini-NK 5µ C18 110A, 250×10, No. 641016-12). The column was perfused at a flow rate of 4.6 mL/min with 65% of (water, 0.1% formic acid)

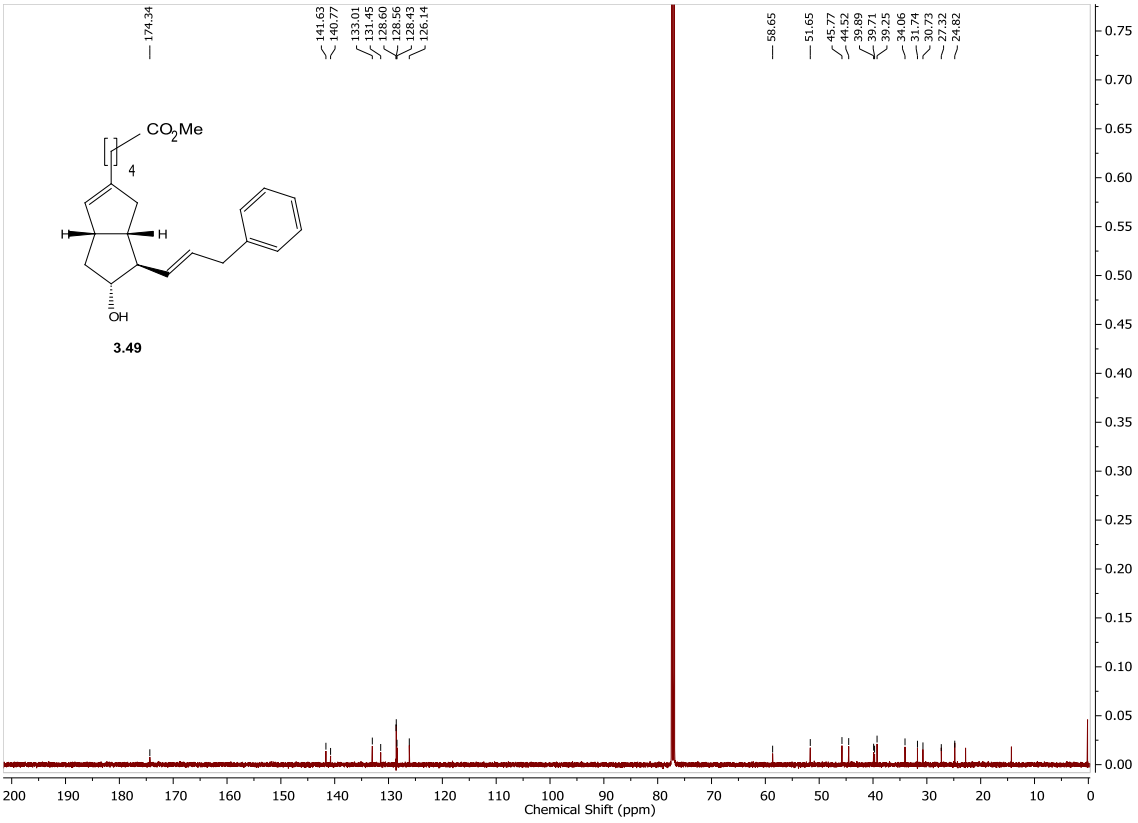
and 35% of CH_3CN over 30 minutes. Product **3.49** was eluted at 16 minutes (1.02 mg, 36%) as a colorless oil. R_f = 0.38 (80:20, hexanes/EtOAc).

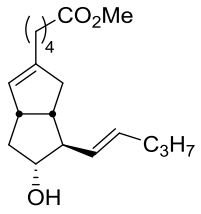
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.27 (m, 2H), 7.22 – 7.18 (m, 3H), 5.71 (dt, J_d = 15.5, J_t = 6.8 Hz, 1H), 5.42 (ddt, J_d = 15.1, 8.5, J_t = 1.6 Hz, 1H), 5.29 – 5.28 (m, 1H), 3.77 (q, *J* = 8.8 Hz, 1H), 3.66 (s, 3H), 3.39 (d, *J* = 6.7 Hz, 2H), 3.04 – 2.96 (m, 1H), 2.46 – 2.40 (m, 1H), 2.37 – 2.26 (m, 3H), 2.05 – 1.99 (m, 3H), 1.93 (q, *J* = 9.2 Hz, 1H), 1.67 – 1.50 (m, 3H), 1.49 – 1.41 (m, 2H), 1.29 (ddd, *J* = 12.4, 9.6, 7.3 Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ 174.3, 141.6, 140.8, 133.0, 131.5, 128.6 (2C), 128.6 (2C), 128.4, 126.1, 58.7, 51.7, 45.8, 44.5, 39.9, 39.7, 39.3, 34.1, 31.7, 30.7, 27.3, 24.8 ppm.

HRMS (ESI) calcd. for $[C_{23}H_{30}O_3+H]^+$: 355.2268, found: 355.2276.


CO2Me
4
H
H
OH
3.49
Chemical Shift (ppm)





3.47

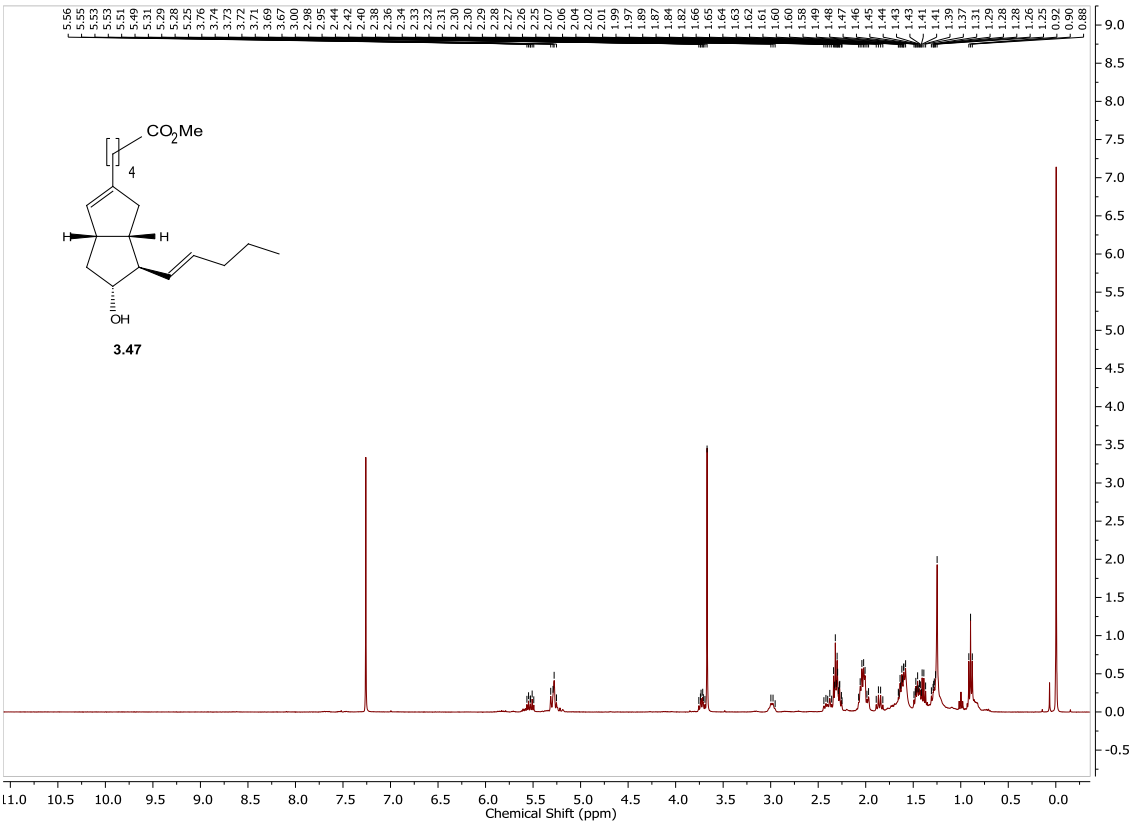
methyl 2-((3a*S*,5*R*,6*R*,6a*S*)-5-hydroxy-6-((*E*)-pent-1-en-1-yl)-1,3a,4,5,6,6a-hexahydropentalen-2-yl)acetate, 3.47

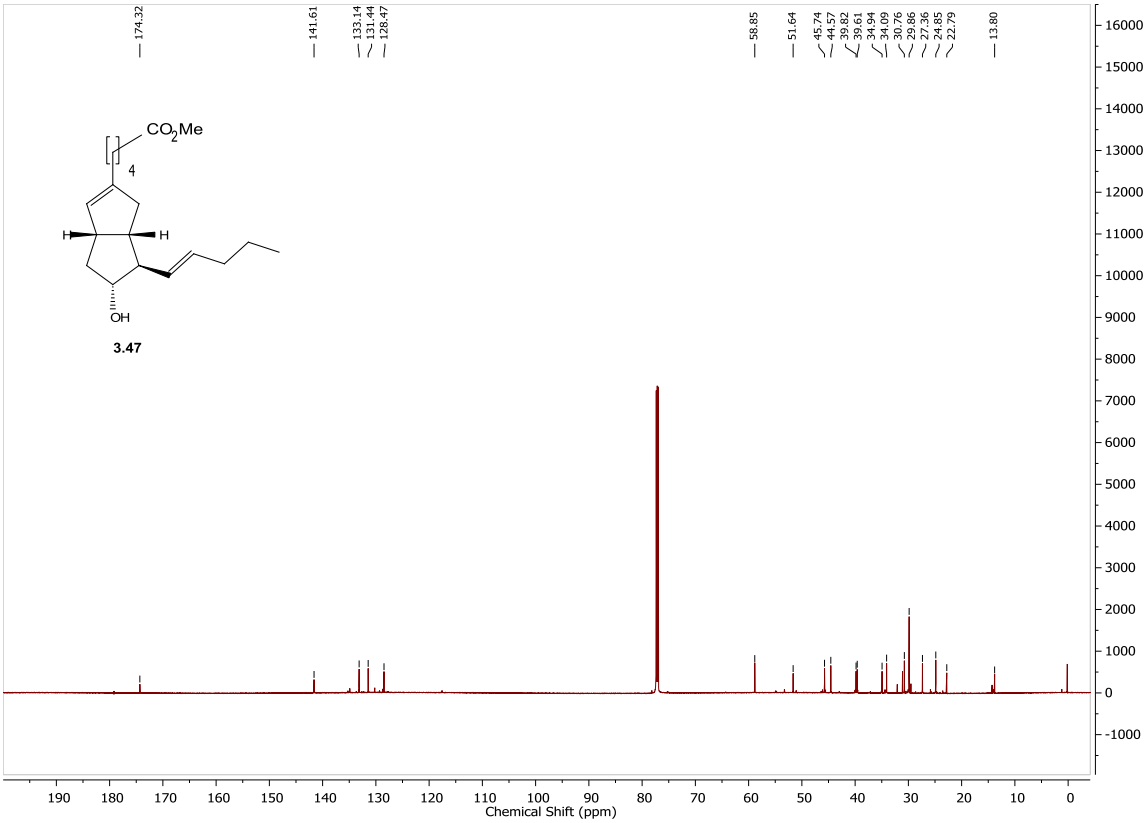
The crude product was purified via silica gel chromatography (90:10, hexanes/EtOAc) to yield ester **3.47** (3.4 mg, 55%) as a colorless oil. R_f = 0.61 (80:20, hexanes/EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.58 – 5.49 (m, 1H), 5.31 – 5.25 (m, 2H), 3.72 (td, J_d = 9.4, J_t = 6.8 Hz, 1H), 3.67 (s, 3H), 2.99 (q, J = 8.9, 7.8 Hz, 1H), 2.44 – 2.36 (m, 1H), 2.36 – 2.23 (m, 4H), 2.07 – 1.97 (m, 4H), 1.85 (q, J = 9.3 Hz, 1H), 1.66 – 1.58 (m, 5H), 1.49 – 1.37 (m, 3H), 1.34 – 1.26 (m, 1H), 0.90 (t, J = 7.3 Hz, 3H) ppm.

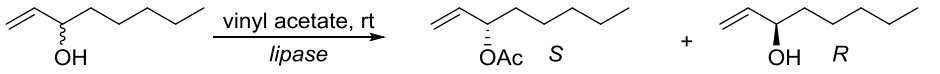
^{13}C NMR (176 MHz, $CDCl_3$) δ 174.3, 141.6, 133.1, 131.4, 128.5, 58.9, 51.6, 45.7, 44.6, 39.8, 39.6, 34.9, 34.1, 30.8, 29.9, 27.4, 24.9, 22.8, 13.8 ppm.

HRMS (ESI) calcd. for $[C_{19}H_{30}O_3+H]^+$: 307.2268, found: 307.2263.

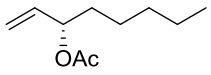




4.2.3 Enzymetic Resolution of 1-octen-3-ol, 3.50



3.50 **3.13**, 37%, 99% *ee* **3.51**, 47%, 99% *ee*

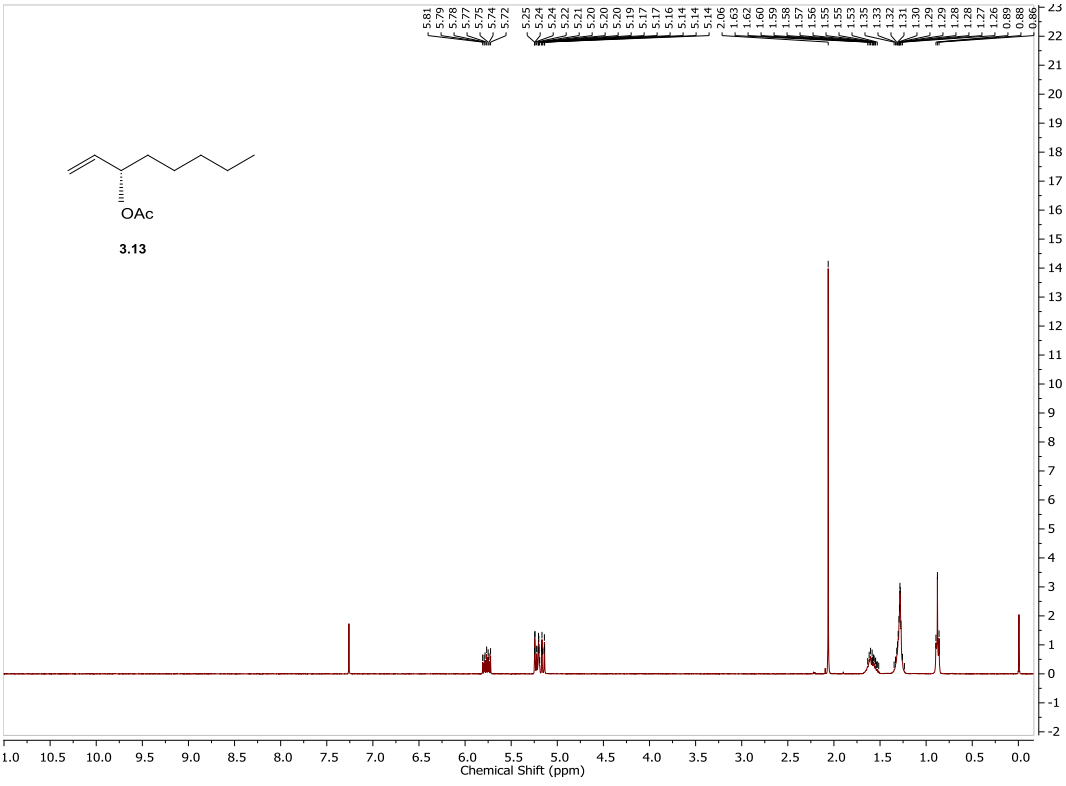


3.13

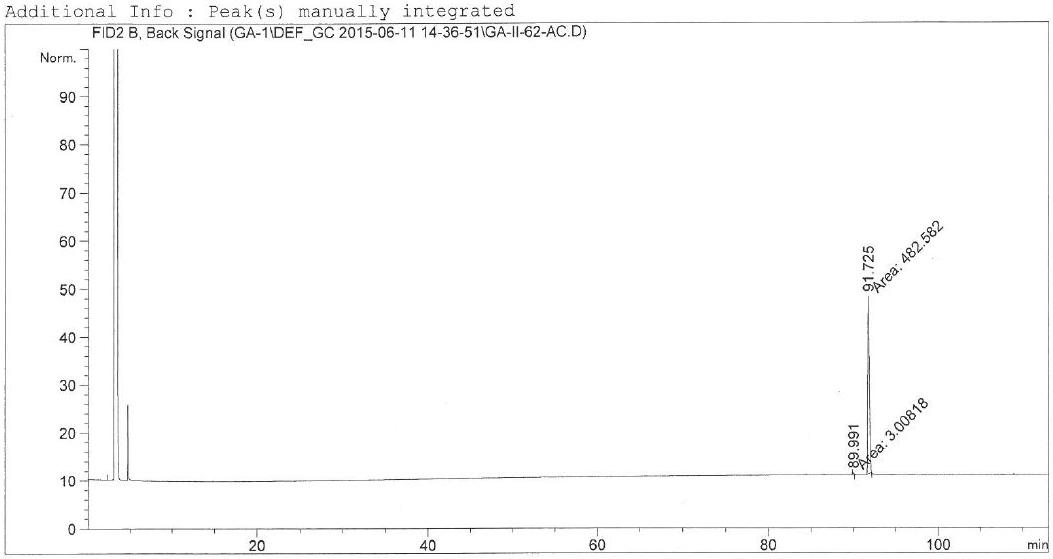
(*S*)-3-acetoxy-1-octene, 3.13

To a stirred solution of racemic 1-octen-3-ol **3.50** (2.0 mL, 13 mmol) in vinyl acetate (22 mL) was added *lipase* (Novozyme® 435, 430 mg). After four hours of stirring, the enzyme was filtered off and washed with diethyl ether. The solution was then concentrated and purified via silica gel chromatography (95:5, hexanes/EtOAc) to yield acetate **3.13** (0.80 g, 37%, 99% *ee*) as a colorless liquid.[42] The enantiomeric excesses were determined using chiral GC analysis. More details are provided in the supplemental information of our previous work.[20]

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.77 (ddd, J = 17.0, 10.5, 6.4 Hz, 1H), 5.24 – 5.14 (m, 2H), 5.15 (dt, J_d = 10.1, J_t = 1.1 Hz, 1H), 2.06 (s, 3H), 1.63 – 1.51 (m, 2H), 1.35 – 1.24 (m, 6H), 0.89 – 0.86 (m, 3H) ppm.

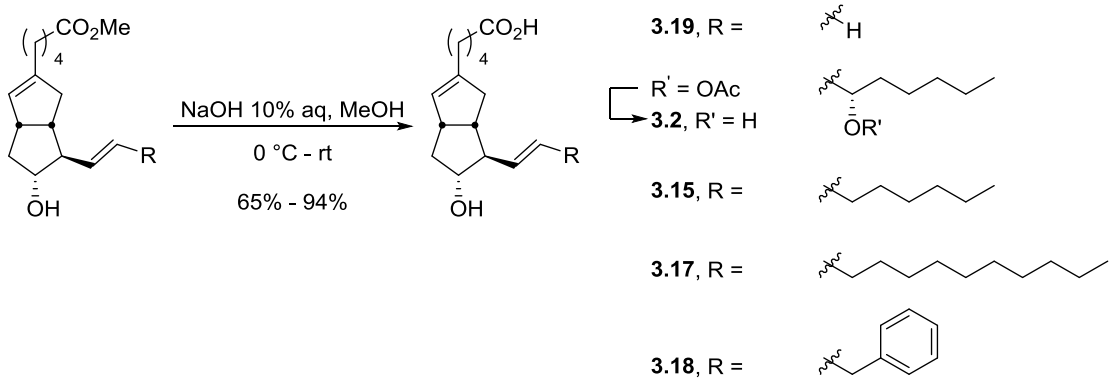


```
================================================================================
Acq. Operator   : GA                                   Seq. Line :   2
Acq. Instrument : GC1                                   Location : Vial 202
Injection Date  : 6/11/2015 3:34:07 PM                      Inj :   1
                                                      Inj Volume : 1 µl
Acq. Method     : C:\CHEM32\1\DATA\GA-1\DEF_GC 2015-06-11 14-36-51\B--40-80-170.EG.M
Last changed    : 5/10/2012 10:44:46 AM by EG
Analysis Method : C:\CHEM32\1\METHODS\DUAL\STANDBY.M
Last changed    : 10/27/2016 12:07:08 PM
                  (modified after loading)
Method Info     : 200 deg for 20 min

Additional Info : Peak(s) manually integrated
```

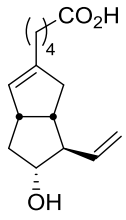



```
================================================================================
                            Area Percent Report
================================================================================

Sorted By             :      Retention Time
Multiplier:                   :      1.0000
Dilution:                     :      1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: FID2 B, Back Signal

Peak RetTime Sig Type    Area      Height     Area
  #   [min]            [pA*s]      [pA]       %
----|-------|---|----|----------|----------|--------|
   1  89.991  1  MM T    3.00818 3.51276e-1  0.61949
   2  91.725  1  MM T  482.58234   37.05834 99.38051

Totals :               485.59052   37.40961
```

4.2.4 General Procedure B for hydrolysis of Analogues, 3.2, 3.15 – 3.19



A 10% NaOH aqueous solution (0.1 M) was added to an analogue methyl ester (1 eq) in MeOH (0.1 M) at 0 °C. The reaction mixture was left to warm to room temperature overnight. The reaction was acidified to pH ~ 2-3 with 10% aqueous HCl, extracted 3x with CH_2Cl_2, dried over Na_2SO_4 and concentrated to give the final analogue.



3.19

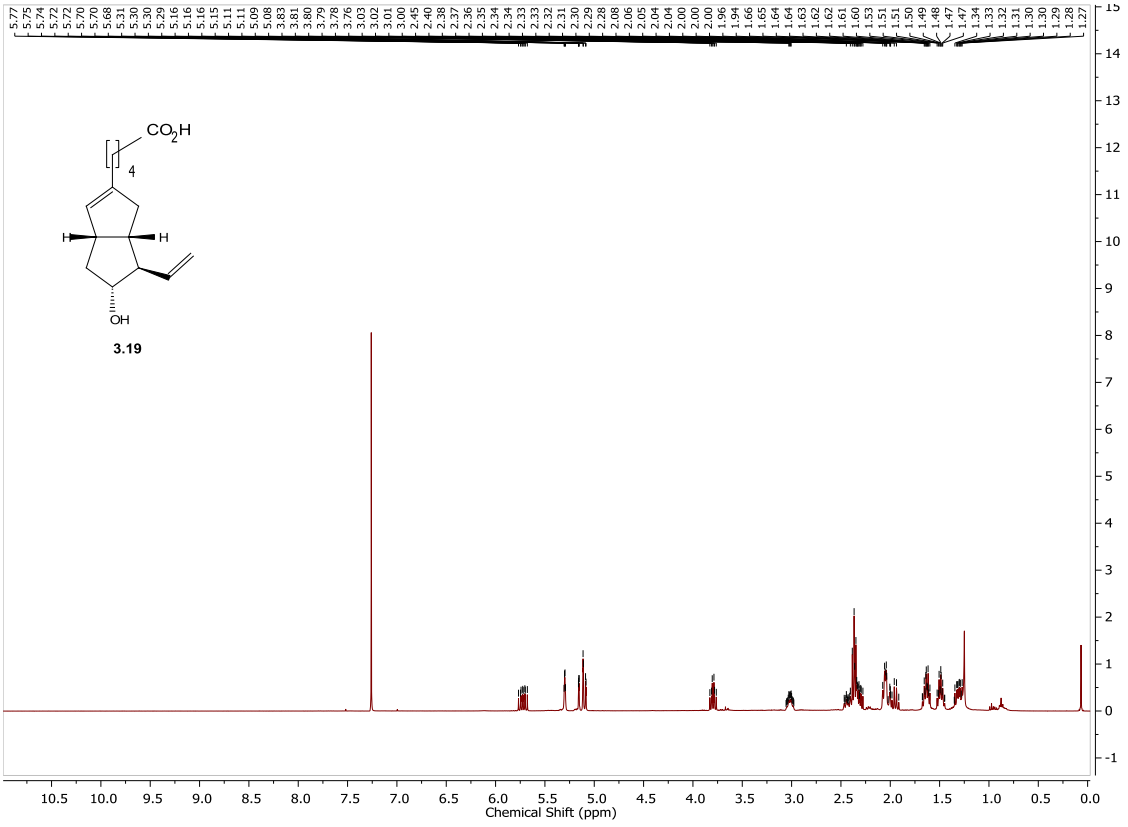
2-((3a*S*,5*R*,6*R*,6a*S*)-5-hydroxy-6-vinyl-1,3a,4,5,6,6a-hexahydropentalen-2-yl)acetic acid, 3.19

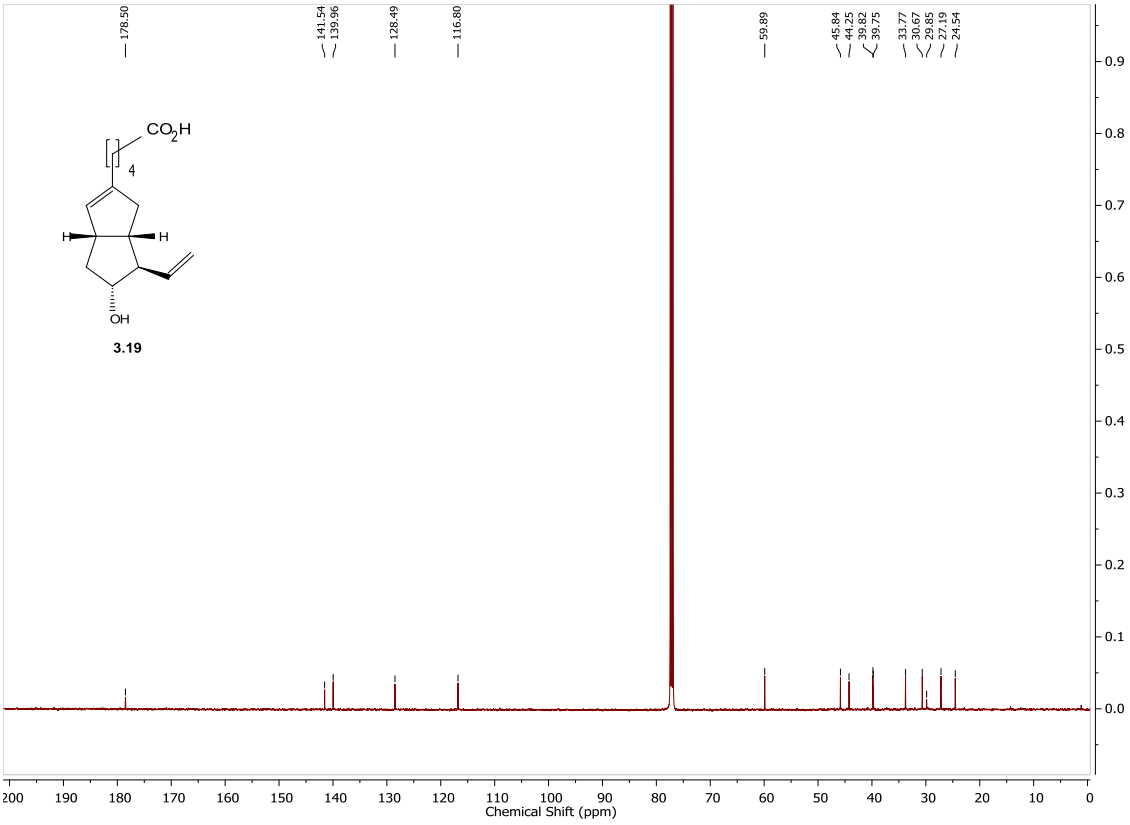
The hydrolysis yielded analogue **3.19** (3.20 mg, 94%) as a colorless solid. R_f = 0.27 (50:50, hexanes/EtOAc).

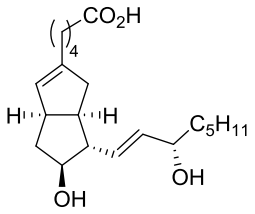
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.72 (ddd, J = 17.0, 10.1, 8.4 Hz, 1H), 5.31 – 5.29 (m, 1H), 5.16 – 6.08 (m, 2H), 3.80 (dt, J_d = 9.5, J_t = 7.0 Hz, 1H), 3.03 – 3.00 (m, 1H), 2.47 – 2.28 (m, 4H), 2.08 – 1.98 (m, 3H), 1.95 (q, J = 9.2 Hz, 1H), 1.67 – 1.60 (m, 2H), 1.53 – 1.45 (m, 2H), 1.35 – 1.27 (m, 2H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ 178.5, 141.5, 139.9, 128.4, 116.8, 59.8, 45.8, 44.2, 39.8, 39.7, 33.7, 30.6, 29.9, 27.1, 24.5 ppm.

HRMS (ESI) calcd. for $[C_{15}H_{22}O_3\text{-}H]^-$: 249.1491, found: 249.1492.







dia-3.2

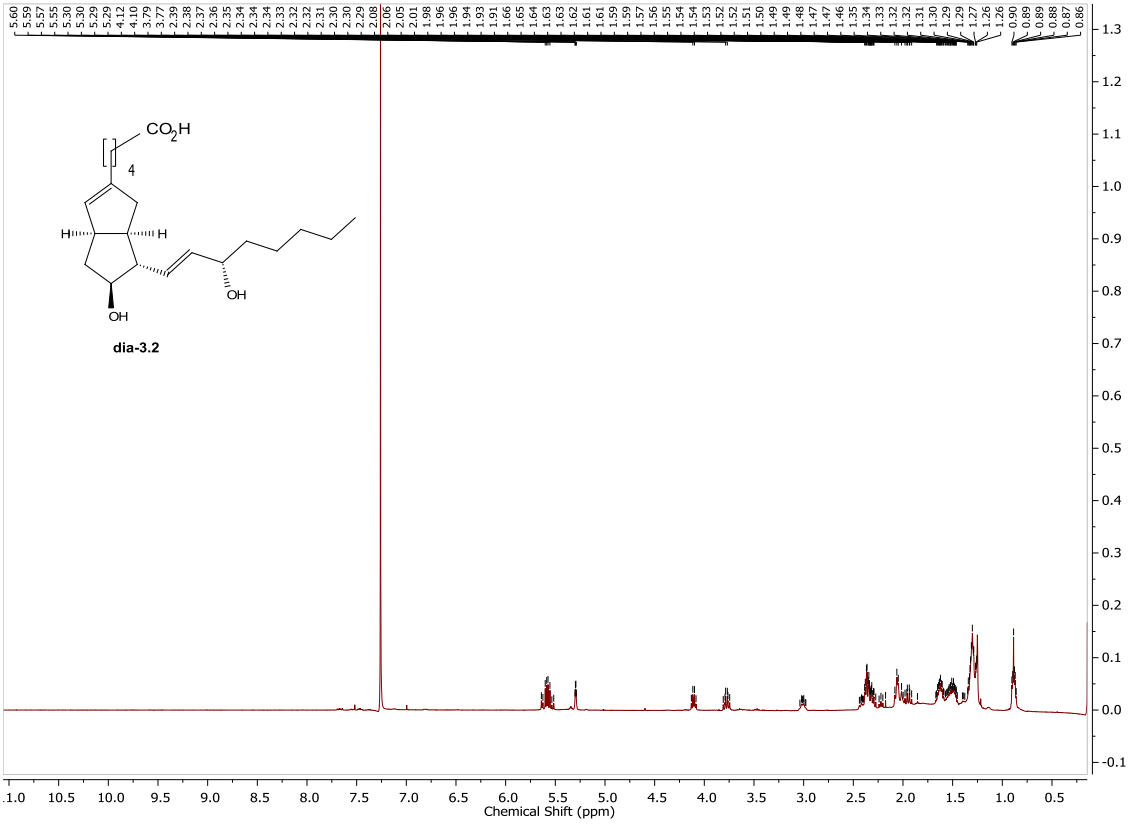
2-((3a*R*,5*S*,6*S*,6a*R*)-5-hydroxy-6-((*S*,*E*)-3-hydroxyoct-1-en-1-yl)-1,3a,4,5,6,6a-hexahydropentalen-2-yl)acetic acid, dia-3.2

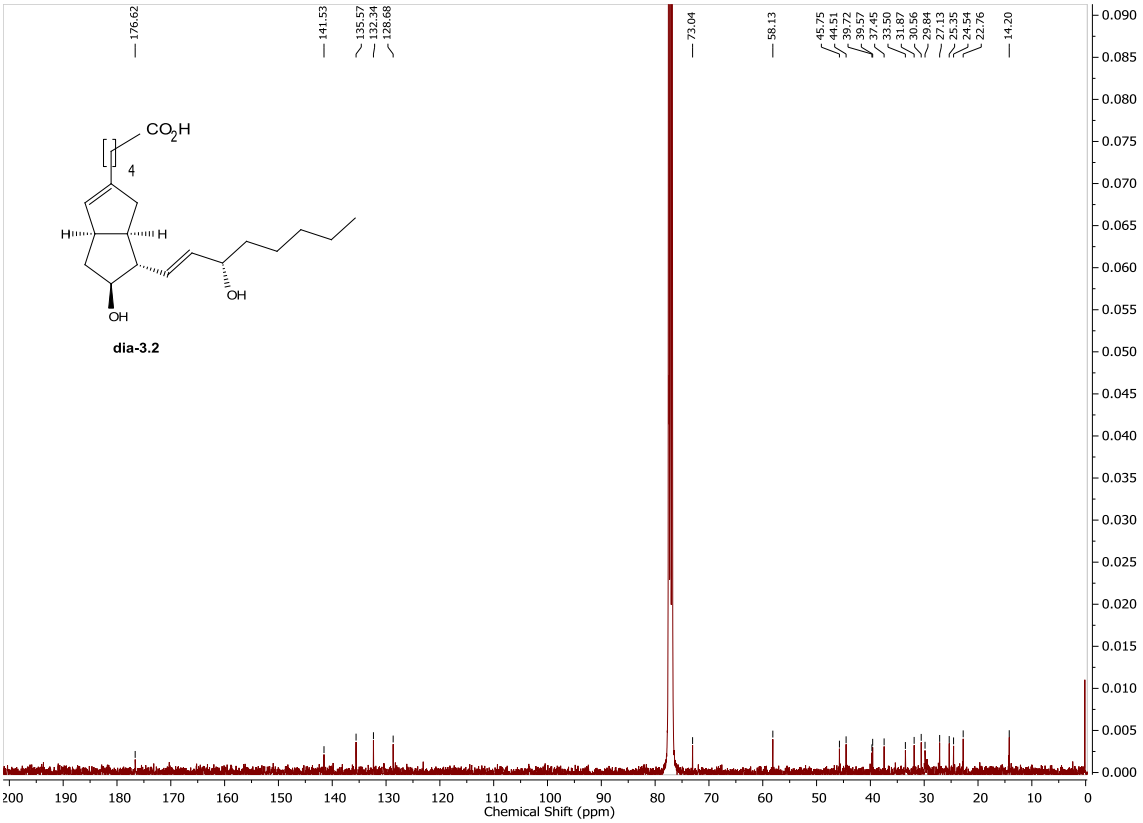
The hydrolysis yielded acid **dia-3.2** (1.52 mg, 65%) as a colorless solid. $R_f = 0.15$ (40:60, hexanes/EtOAc).

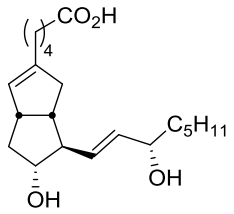
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.64 – 5.52 (m, 2H), 5.30 – 5.29 (m, 1H), 5.23 (q, J = 6.5 Hz, 1H), 3.78 (dt, J_d = 9.5, J_t = 7.1 Hz, 1H), 3.04 – 2.98 (m, 1H), 2.44 – 2.18 (m, 6H), 2.08 – 1.98 (m, 2H), 1.98 – 1.91 (m, 2H), 1.67 – 1.57 (m, 4H), 1.57 – 1.45 (m, 2H), 1.36 – 1.26 (m, 6H), 0.90 – 0.86 (m, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 176.6, 141.5, 135.6, 132.3, 128.7, 73.0, 58.1, 45.8, 44.5, 39.7, 39.67, 37.5, 33.5, 31.9, 30.6, 29.8, 27.1, 25.4, 24.5, 22.8, 14.2 ppm.

HRMS (ESI) calcd. for $[C_{21}H_{34}O_4\text{-}H]^-$: 349.2379, found: 349.2375.







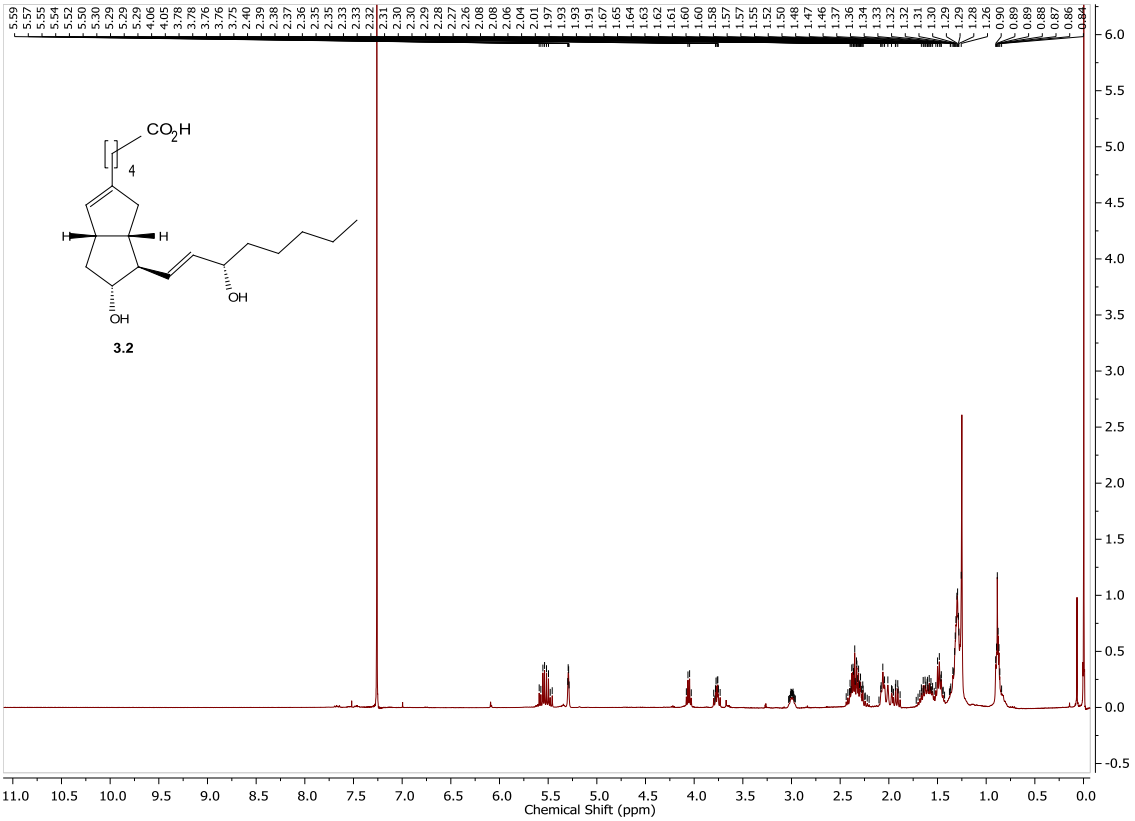
3.2

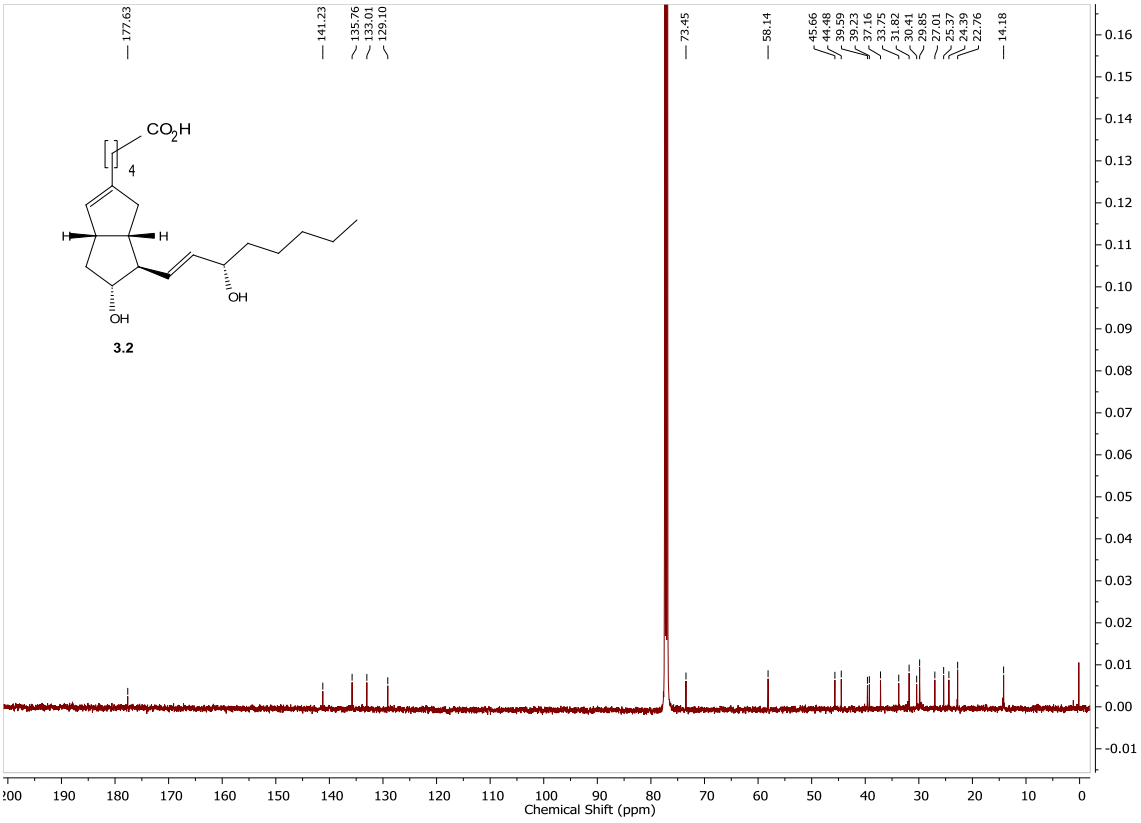
Isocarbacyclin, 3.2

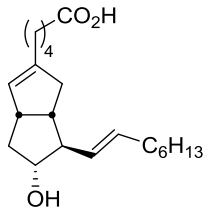
The hydrolysis yielded isocarbacyclin **3.2** (1.50 mg, 68%) as a colorless solid. R_f = 0.15 (40:60, hexanes/EtOAc). ^{1}H and ^{13}C NMR are consistent with literature reports.[24,25]

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.59 – 5.46 (m, 2H), 5.30 – 5.29 (m, 1H), 4.06 (q, *J* = 6.7 Hz, 1H), 3.80 – 3.73 (m, 1H), 3.03 – 2.96 (m, 1H), 2.44 – 2.20 (m, 6H), 2.10 – 1.88 (m, 5H), 1.72 – 1.55 (m, 3H), 1.53 – 1.43 (m, 2H), 1.38 – 1.26 (m, 6H), 0.90 – 0.84 (m, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ 177.6, 141.2, 135.8, 133.0, 129.1, 73.45, 58.1, 45.7, 44.5, 39.6, 39.2, 37.2, 33.8, 31.8, 30.4, 29.9, 27.0, 25.4, 24.4, 22.8, 14.2 ppm.







3.15

Deoxy-isocarbacyclin, 3.15

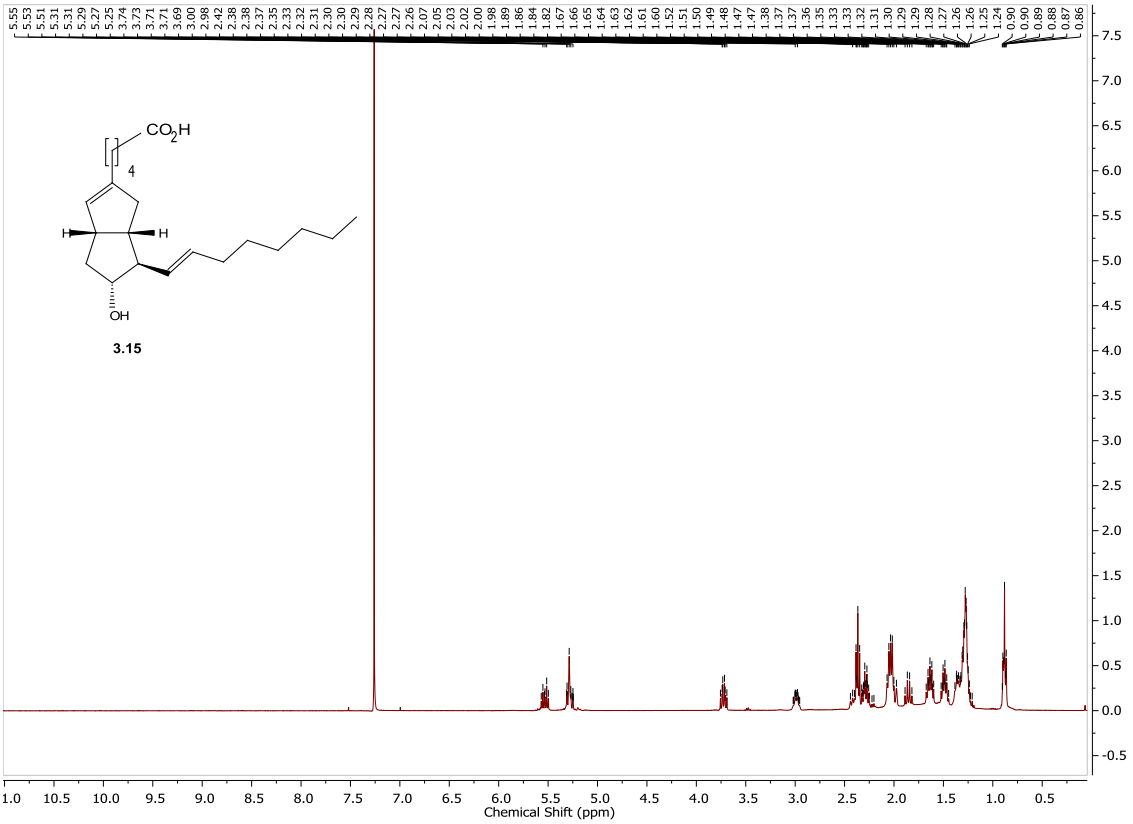
The hydrolysis yielded *deoxy*-isocarbacyclin **3.15** (1.68 mg, 83%) as a colorless solid. R_f = 0.23 (70:30, hexanes/EtOAc).

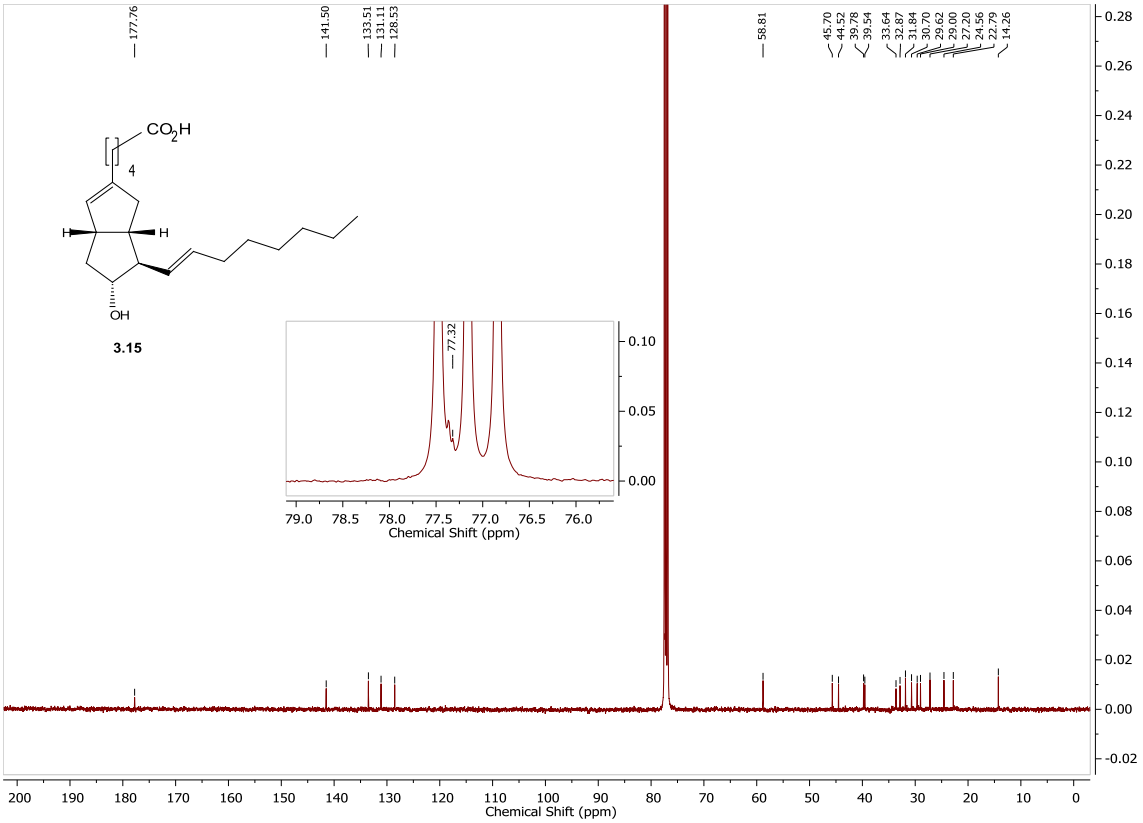
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.54 (dt, J_d = 15.4, J_t = 6.7 Hz, 1H), 5.31 – 5.24 (m, 2H), 3.72 (dt, J_d = 9.6, J_t = 7.0 Hz, 1H), 3.02 – 2.95 (m, 1H), 2.44 – 2.35 (m, 3H), 2.33 – 2.20

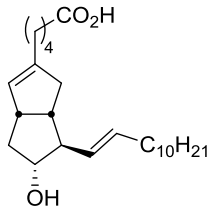
(m, 2H), 2.07 – 1.98 (m, 5H), 1.85 (q, J = 9.3 Hz, 1H), 1.64 (dt, J_d = 15.1, J_t = 7.2 Hz, 2H), 1.52 – 1.45 (m, 2H), 1.38 – 1.21 (m, 9H), 0.90 – 0.86 (m, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 177.8, 141.5, 133.5, 131.1, 128.5, 77.3, 58.8, 45.7, 44.5, 39.8, 39.5, 33.6, 32.9, 31.8, 30.7, 29.6, 29.0, 27.2, 24.6, 22.8, 14.3 ppm.

HRMS (ESI) calcd. for $[C_{21}H_{34}O_3\text{-}H]^-$: 333.2430, found: 333.2434.







3.17

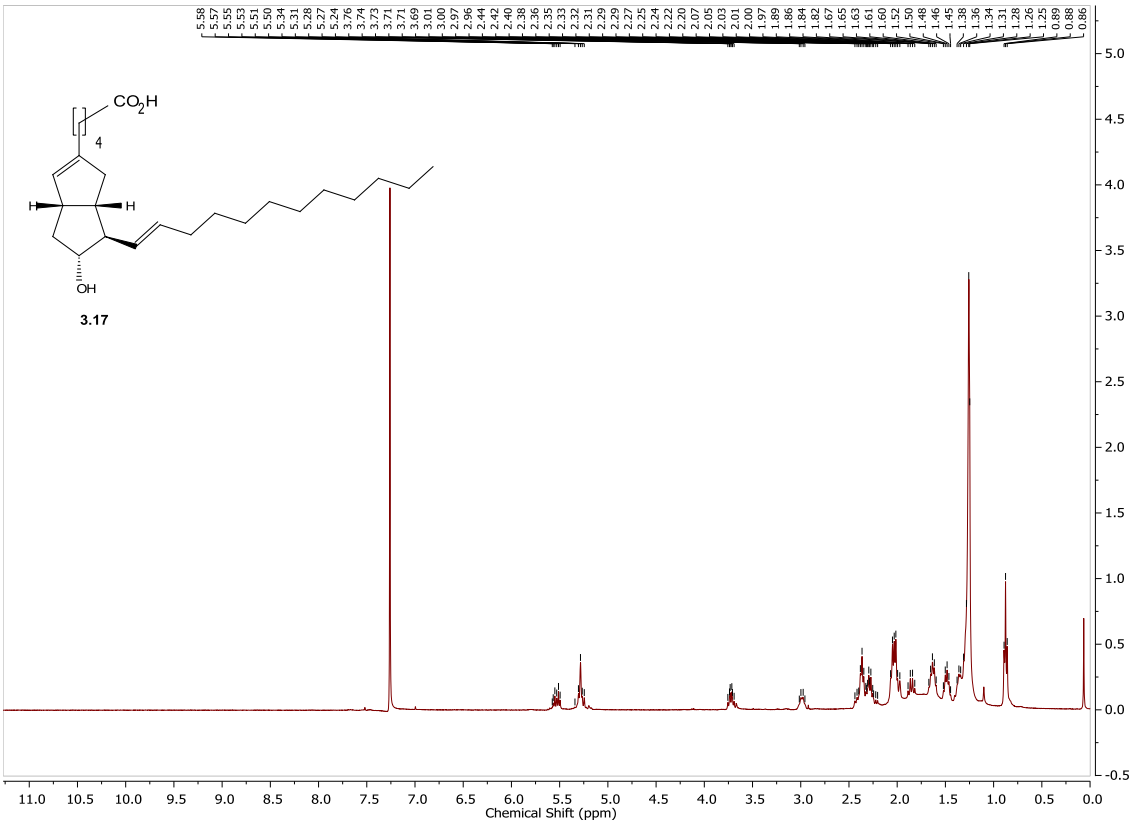
2-((3a*S*,5*R*,6*R*,6a*S*)-6-((*E*)-dodec-1-en-1-yl)-5-hydroxy-1,3a,4,5,6,6a -hexahydropentalen-2-yl)acetic acid, 3.17

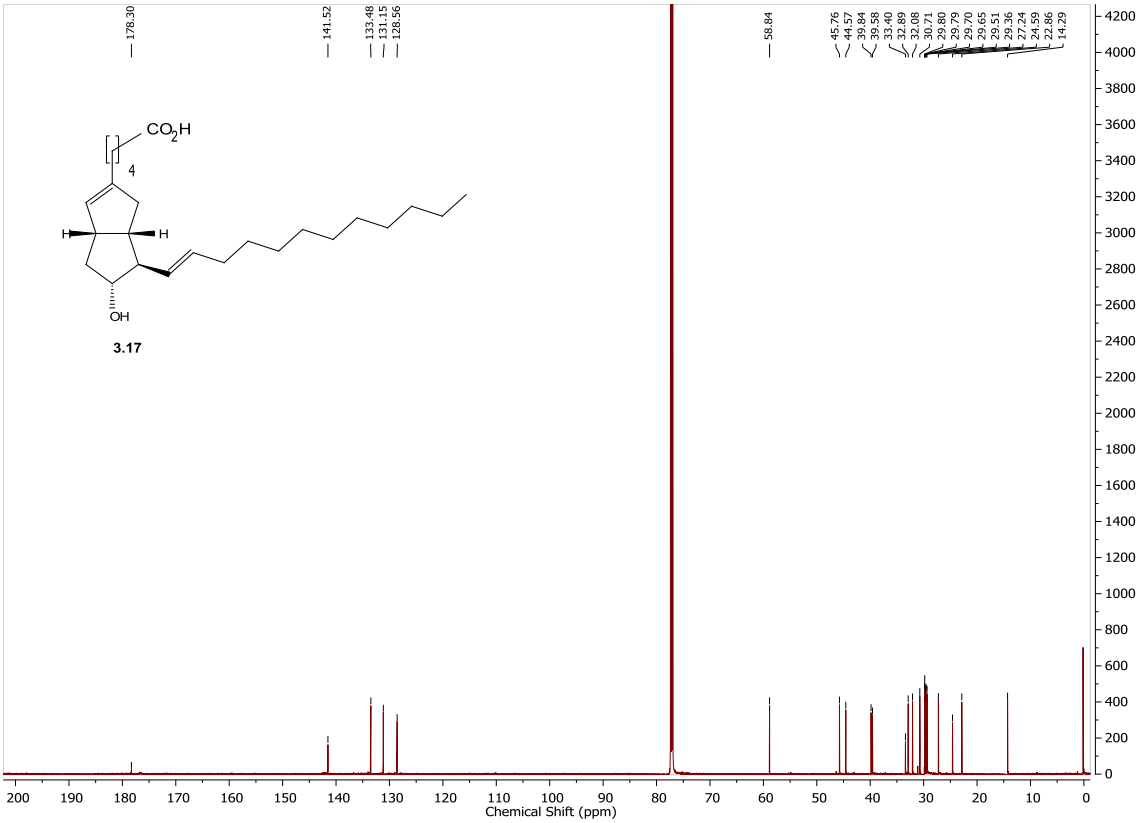
The hydrolysis yielded analogue **3.17** (2.02 mg, 90%) as a beige solid. $R_f = 0.23$ (80:20, hexanes/EtOAc).

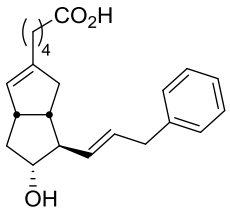
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.53 (dt, J_d = 14.1, J_t = 6.7 Hz, 1H), 5.34 – 5.24 (m, 2H), 3.72 (dt, J_d = 9.5, J_t = 6.8 Hz, 1H), 3.01 – 2.96 (m, 1H), 2.44 – 2.20 (m, 5H), 2.07 – 1.97 (m, 5H), 1.85 (q, J = 9.3 Hz, 1H), 1.67 – 1.60 (m, 2H), 1.52 – 1.45 (m, 2H), 1.38 – 1.25 (m, 17H), 0.88 (t, J = 6.5 Hz, 3H) ppm.

^{13}C NMR (176 MHz, $CDCl_3$) δ 178.3, 141.5, 133.5, 131.2, 128.6, 58.8, 45.8, 44.6, 39.9, 39.6, 33.4, 32.9, 32.1, 30.7, 29.8, 29.8, 29.8, 29.7, 29.7, 29.5, 29.4, 27.2, 24.6, 22.9, 14.29 ppm.

HRMS (ESI) calcd. for $[C_{25}H_{42}O_3\text{-}H]^-$: 391.3056, found: 391.3063.







3.18

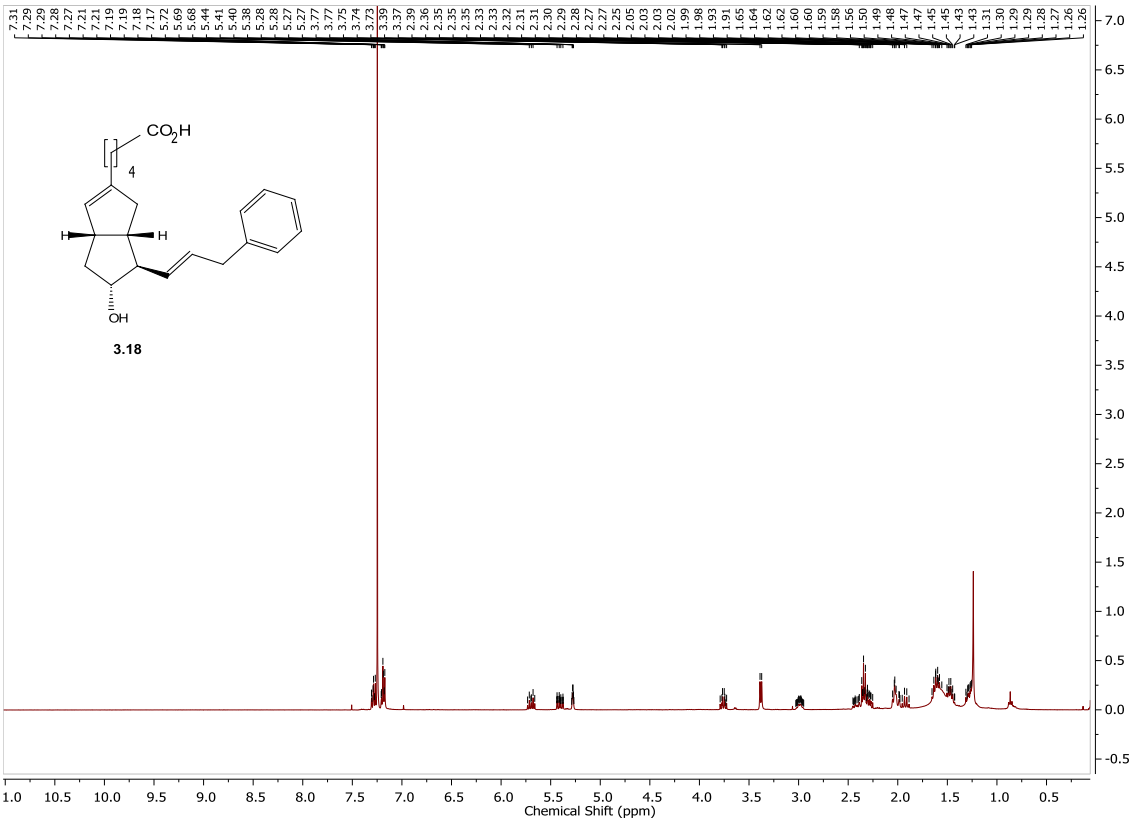
2-((3a*S*,5*R*,6*R*,6a*S*)-5-hydroxy-6-((*E*)-3-phenylprop-1-en-1-yl)-1,3a,4,5,6,6a-hexahydropentalen-2-yl)acetic acid, 3.18

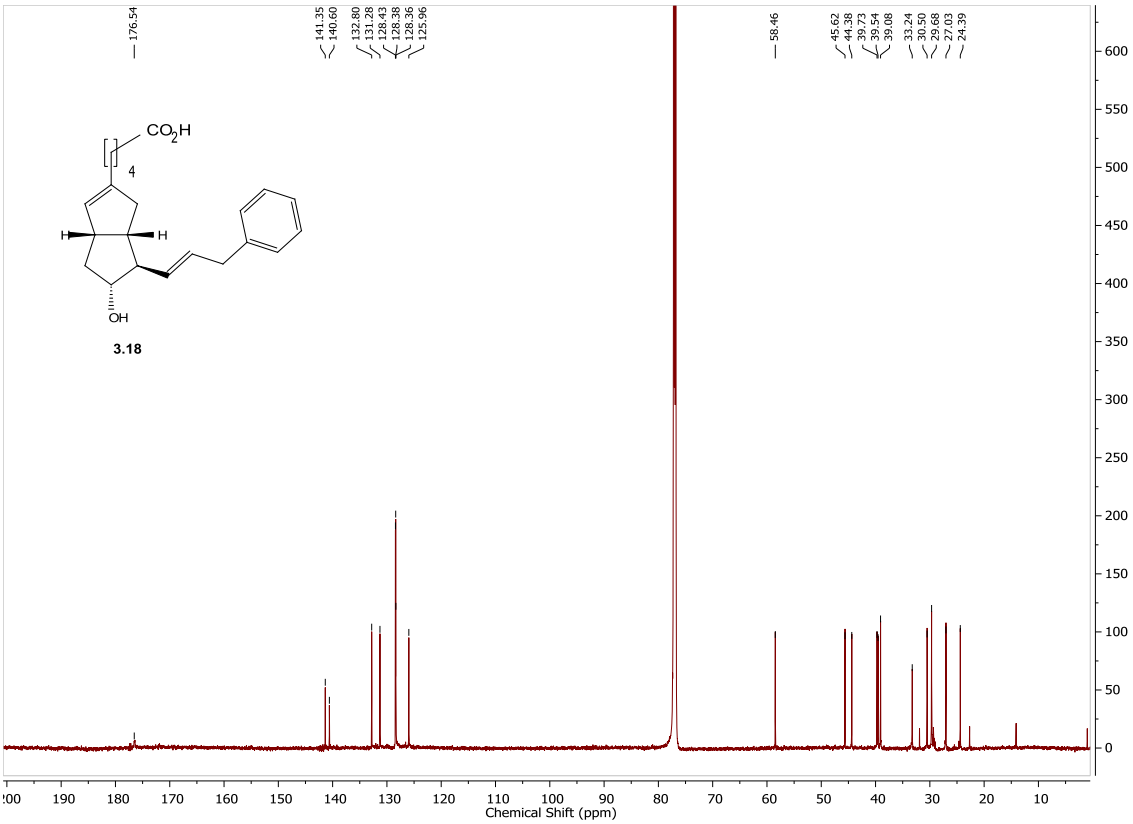
The hydrolysis yielded analogue **3.18** (0.80 mg, 84%) as a colorless solid. R_f = 0.36 (50:50, hexanes/EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (dd, J = 8.5, 6.7 Hz, 2H), 7.22 – 7.16 (m, 3H), 5.70 (dt, J_d = 15.4, J_t = 6.8 Hz, 1H), 5.73 – 5.66 (ddt, J_d = 15.5, 8.6, J_t = 1.4 Hz, 1H), 5.28 – 5.27 (m, 1H), 3.76 (td, J_d = 9.5, J_t = 7.0 Hz, 1H), 3.38 (d, J = 6.7 Hz, 2H), 3.03 – 2.95 (m, 1H), 2.52 – 2.45 (m, 5H), 2.05 – 1.98 (m, 3H), 1.92 (q, J = 9.2 Hz, 1H), 1.65 – 1.43 (m, 3H), 1.31 – 1.26 (m, 2H) ppm.

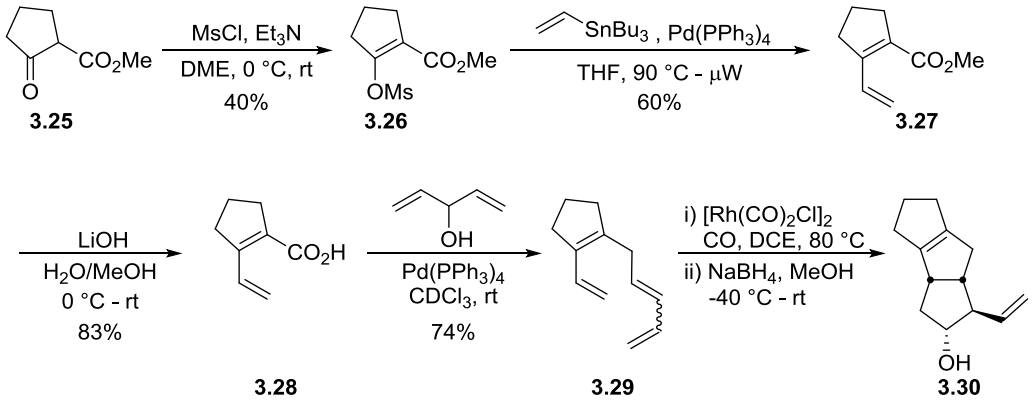
^{13}C NMR (176 MHz, $CDCl_3$) δ 176.5, 141.4, 140.6, 132.8, 131.28, 128.4 (4C), 128.4, 126.0, 58.5, 45.6, 44.4, 39.7, 39.5, 39.1, 33.2, 30.5, 29.7, 27.0, 24.4.

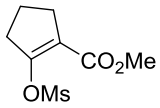
HRMS (ESI) calcd. for $[C_{22}H_{28}O_3\text{-}H]^-$: 339.1960, found: 339.1967.





4.3 Synthesis of Tricyclic Core (3.30) in the Model System



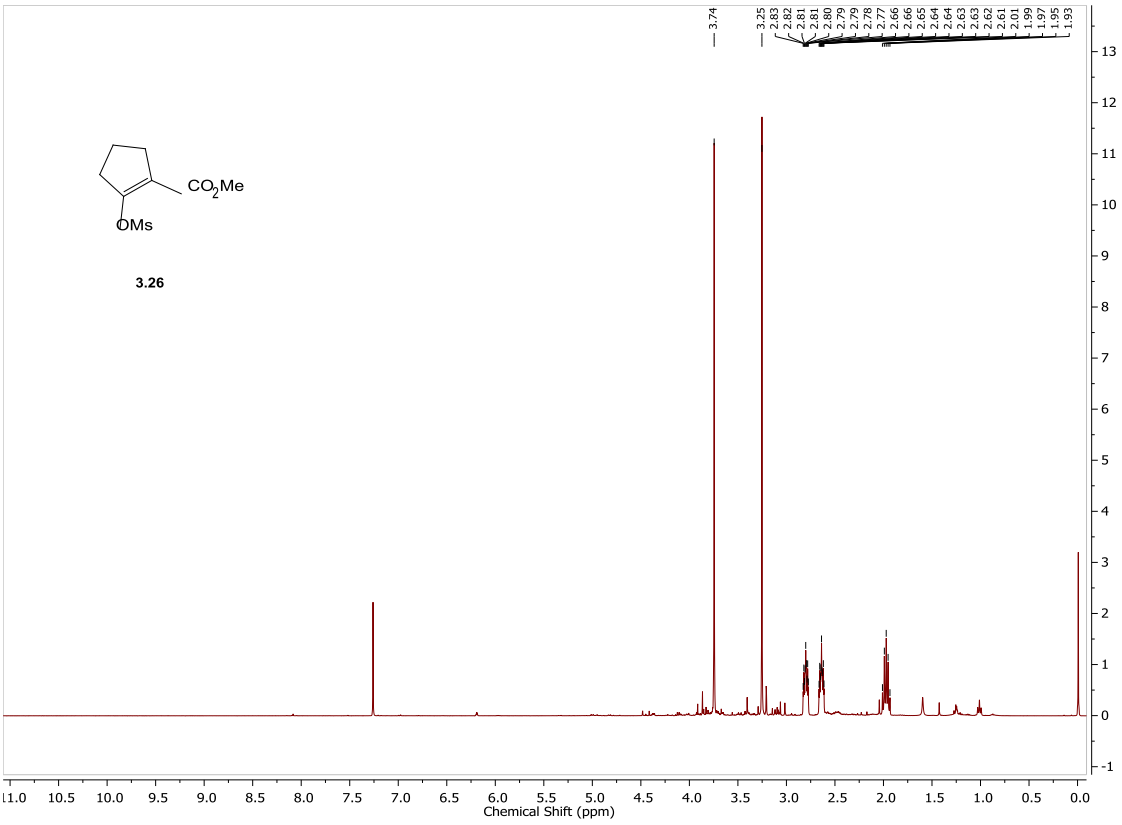


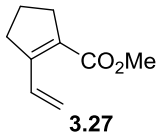
3.26

Methyl 2-((methylsulfonyl)oxy)cyclopent-1-enecarboxylate, 3.26

Following a previously reported procedure, mesylate **3.26** was synthesized as a brown oil (434 mg, 40% yield). R_f = 0.29 (70:30, hexanes/EtOAc). ^{1}H and ^{13}C NMR are consistent with literature reports.[39]

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.74 (s, 3H), 3.25 (s, 3H), 2.80 (tt, *J* = 8.0, 2.7 Hz, 1H), 2.64 (tt, *J* = 7.7, 2.6 Hz, 2H) 1.97 (quint, *J* = 7.8 Hz, 2H) ppm.



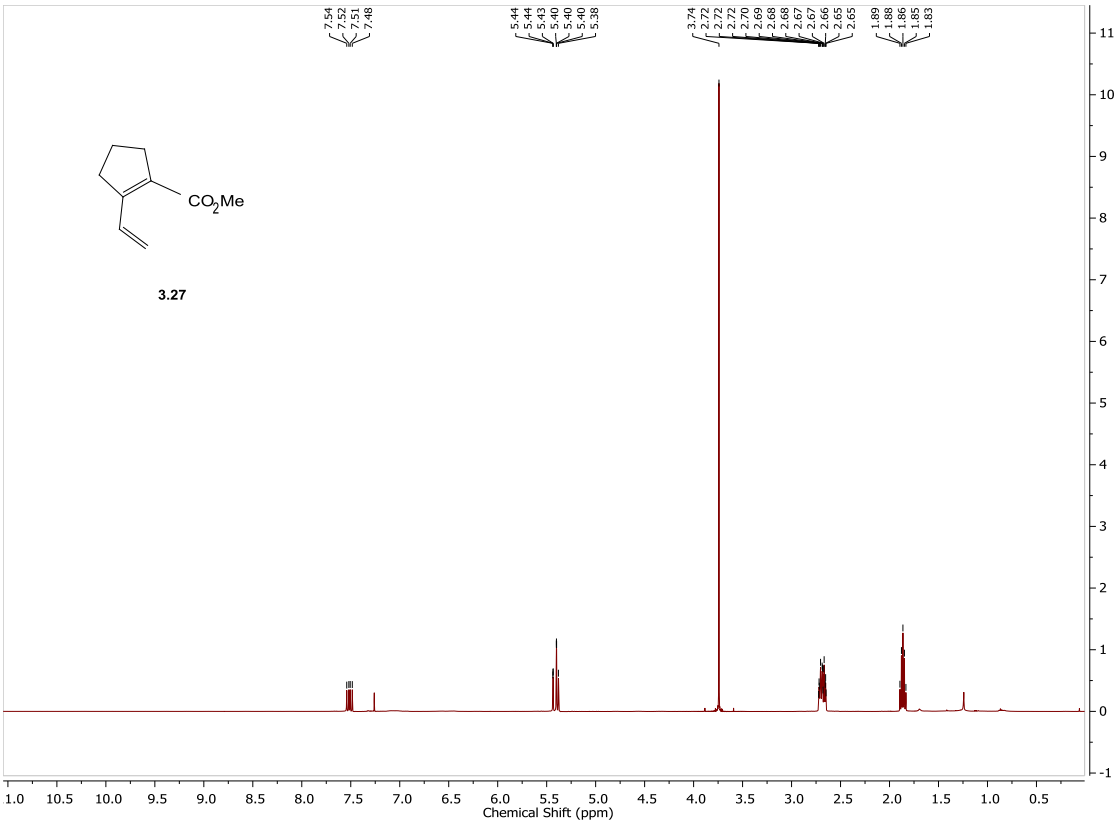


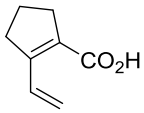
3.27

Methyl 2-vinylcyclopent-1-ene-1-carboxylate, 3.27

To a solution of LiBr (356 mg, 4.1 mmol) and $Pd(PPh_3)_4$ (316 mg, 0.27 mmol) in THF (17 mL) was added a solution of mesylate **3.26** (600 mg, 2.7 mmol) and vinyltributylstannane (1.6 mL, 5.9 mmol) in THF (10 mL) under an atmosphere of N_2. The solution was heated in a microwave reactor at 90 °C for 24 hours, cooled to room temperature, diluted with CH_2Cl_2 and washed with water. The aqueous layer was back extracted with CH_2Cl_2, and the combined organic layers were washed with 10% NH_4OH solution, water and saturated aqueous NaCl, dried over Na_2SO_4 and concentrated. Purification via silica gel chromatography (97:2, hexanes/diethyl ether) yielded ester **3.27** (250 mg, 60%) as a colorless oil. R_f = 0.52 (90:10, hexanes/EtOAc). ^{1}H and ^{13}C NMR are consistent with literature reports.[43]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.44 – 5.38 (m, 2H), 3.74 (s, 3H), 2.72 – 2.65 (m, 4H), 1.86 (quint, *J* = 7.6 Hz, 2H) ppm.



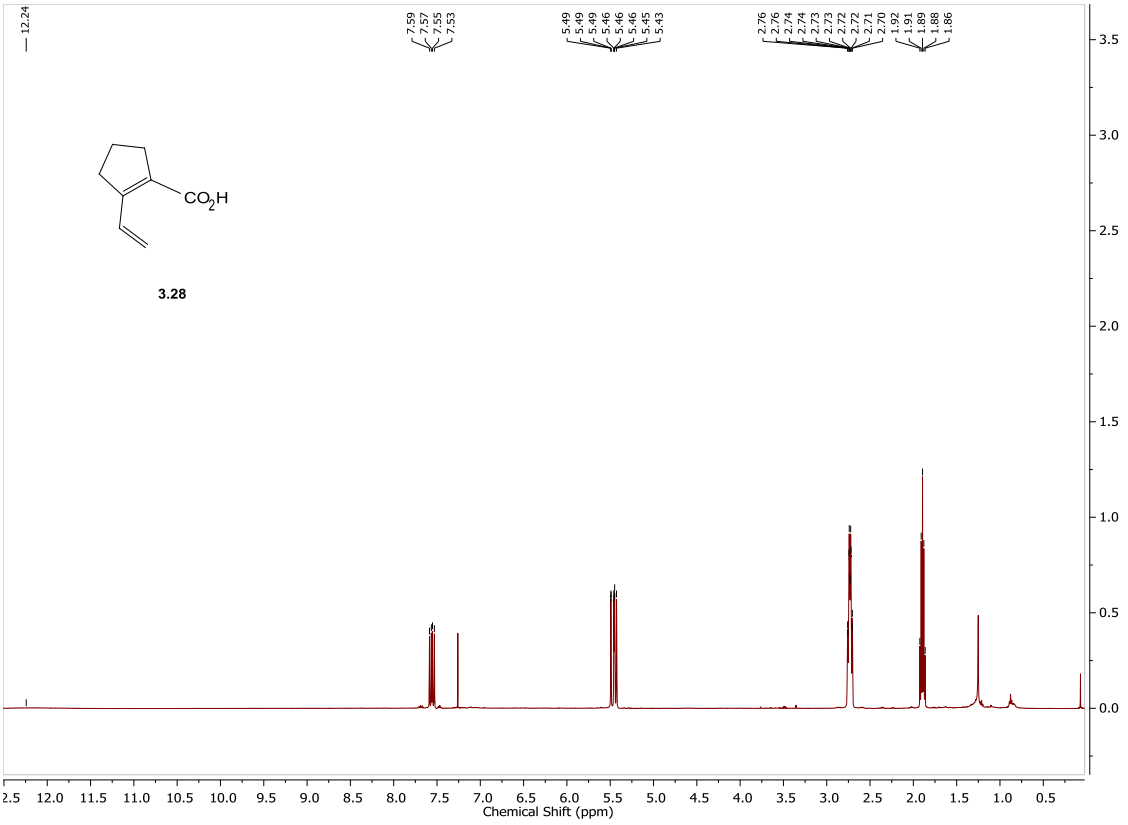


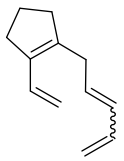
3.28

2-Ethenyl-1-cyclopentenecarboxylic Acid, 3.28

Following a previously reported procedure, acid **3.28** was synthesized as an off-white solid (38 mg, 83% yield). R_f = 0.90 (89:10:1, hexanes/EtOAc/AcOH). ^{1}H and ^{13}C NMR are consistent with literature reports.[41,43]

^{1}H NMR (400 MHz, $CDCl_3$) δ 12.24 (bs, 1H), 7.56 (dd, J = 17.6, 10.8 Hz, 1H), 5.47 (dt, J_d = 17.6 Hz, J_t = 0.6 Hz, 1H), 5.44 (d, J = 10.8 Hz, 1H), dtd (J_d = 9.8, 1.6, J_t = 7.8, 4H), 1.89 (quint, J = 7.7 Hz, 2H) ppm.





3.29

(*E*,*Z*)-1(penta-2,4-dien-1-yl)-2-vinylcyclopent-1-ene, 3.29

A microwave vial with dienoic acid **3.29** (16 mg, 0.12 mmol), pentadienyl substrate 1,4-pentadien-3-ol **3.4** (13 µL, 0.14 mmol) and water (2.5 µL, 0.14 mmol) in $CDCl_3$ (1.1 mL) was capped with a septum, and purged with N_2. Tris(dibenzylideneacetone)dipalladium(0)-chloroform adduct (5.9 mg, 0.0057 mmol) and PPh_3 (6.0 mg, 0.023 mmol) were dissolved in $CDCl_3$ (0.1 mL) and added to the mixture.

The mixture was left at room temperature under a balloon of N_2 for 48 hours. The solution was concentrated and purified via silica gel chromatography (pentane) to yield tetraene **3.29** (15 mg, 74% yield) as a colorless oil. R_f (mixture of diastereomers) = 0.91 (hexanes). The product is a mixture of two diastereomers in a 1.85:1 ratio.

Mixture of two inseparable diastereomers

Diastereomer A (major):

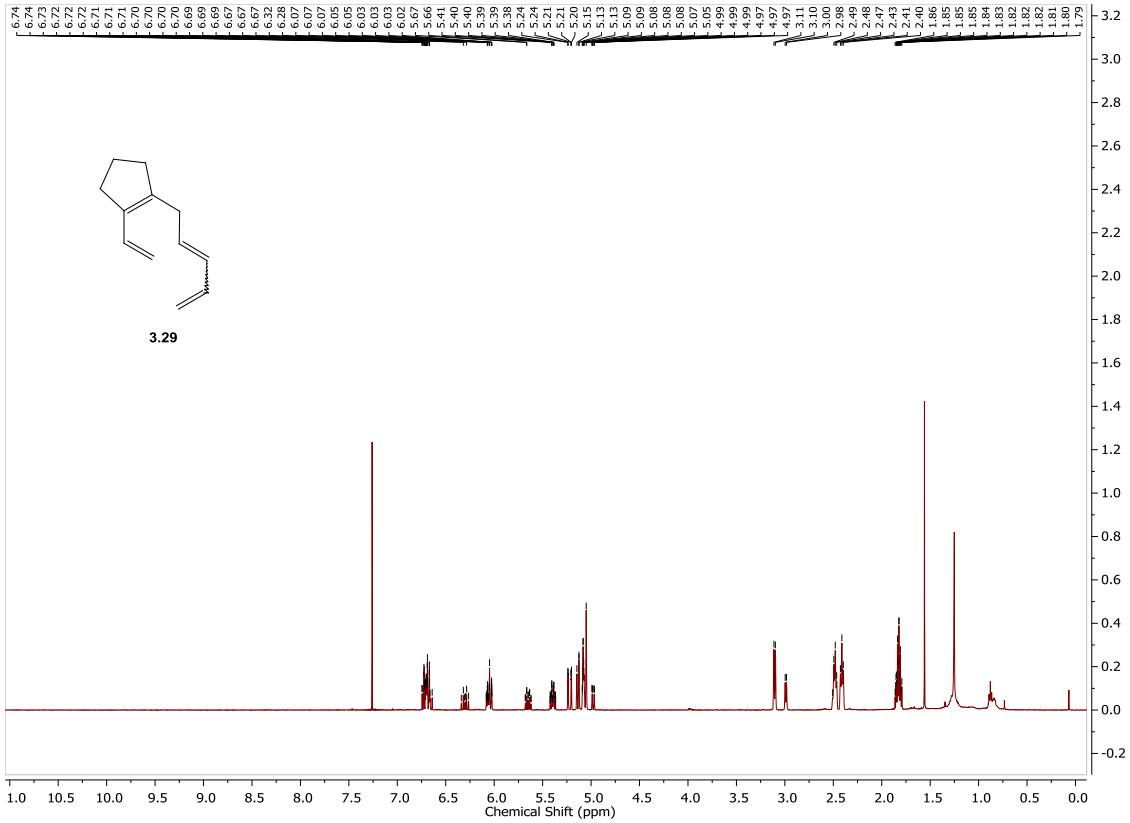
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.74 – 6.64 (m, 2H) 6.07 – 6.02 (m, 2H), 5.42 – 5.37 (m, 1H), 5.15 – 5.13 (m, 1H), 5.09 – 5.05 (m, 2H), 3.11 (d, J = 7.7 Hz, 2H), 2.47 – 2.51 (m, 2H), 2.40 – 2.43 (m, 2H), 1.79 – 1.86 (m, 2H) ppm.

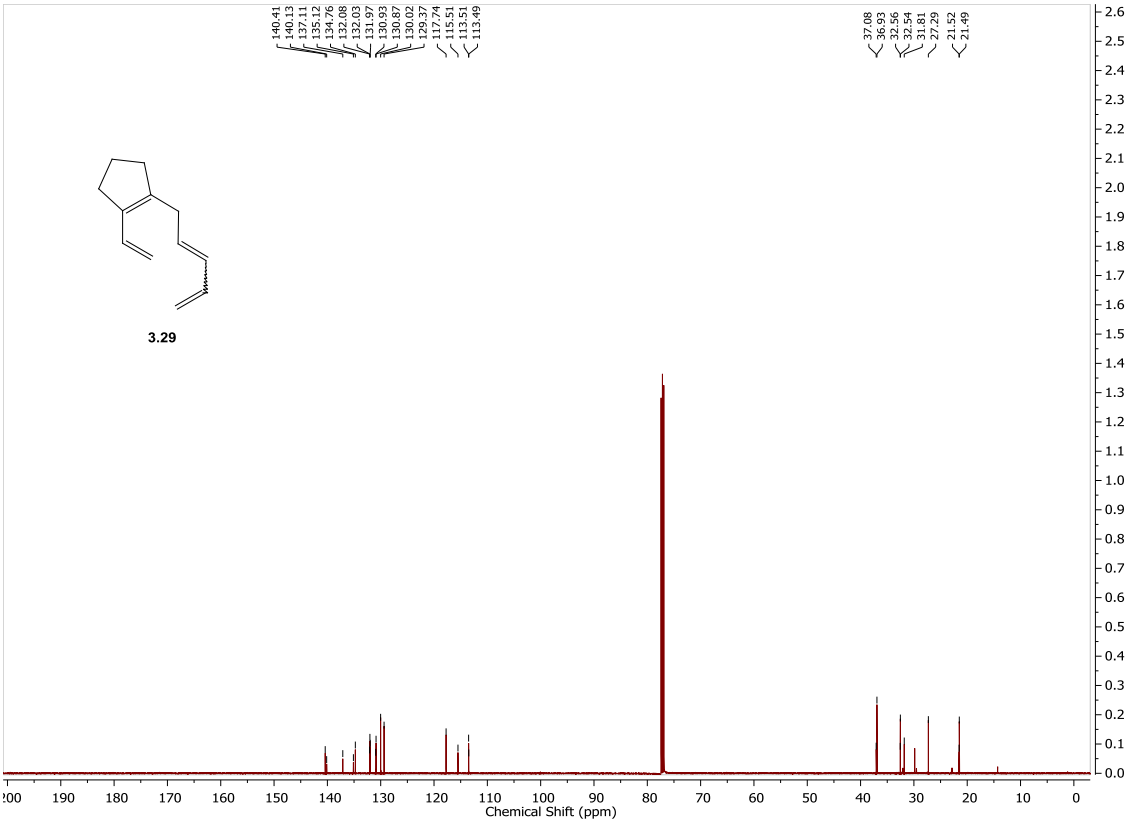
Diastereomer B (minor):

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.74 – 6.64 (m, 1H), 6.30 (dt, J_d = 17.0, J_t = 10.3 Hz, 1H), 5.68 - 5.62 (m, 1H), 5.42 – 5.37 (m, 1H), 5.24 – 5.20 (m, 2H), 5.15 – 5.13 (m, 1H), 4.97 – 4.99 (m, 1H), 2.99 (d, J = 7.1 Hz, 2H), 2.47 – 2.51 (m, 2H), 2.40 – 2.43 (m, 2H), 1.79 – 1.86 (m, 2H) ppm.

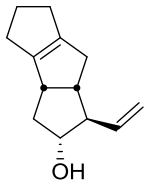
^{13}C NMR (125 MHz, $CDCl_3$) δ 140.4, 140.1, 137.1, 135.1, 134.7, 132.1, 132.0, 131.9, 130.9, 130.8, 130.0, 129.3, 117.7, 115.5, 113.5, 113.5, 37.1, 36.9, 32.5, 32.5, 31.8, 27.2, 21.5, 21.5. ppm.

HRMS (APPI) calcd. for $[C_{12}H_{16}]^+$: 161.1330, found: 161.1323.


3.29
Chemical Shift (ppm)



3.29



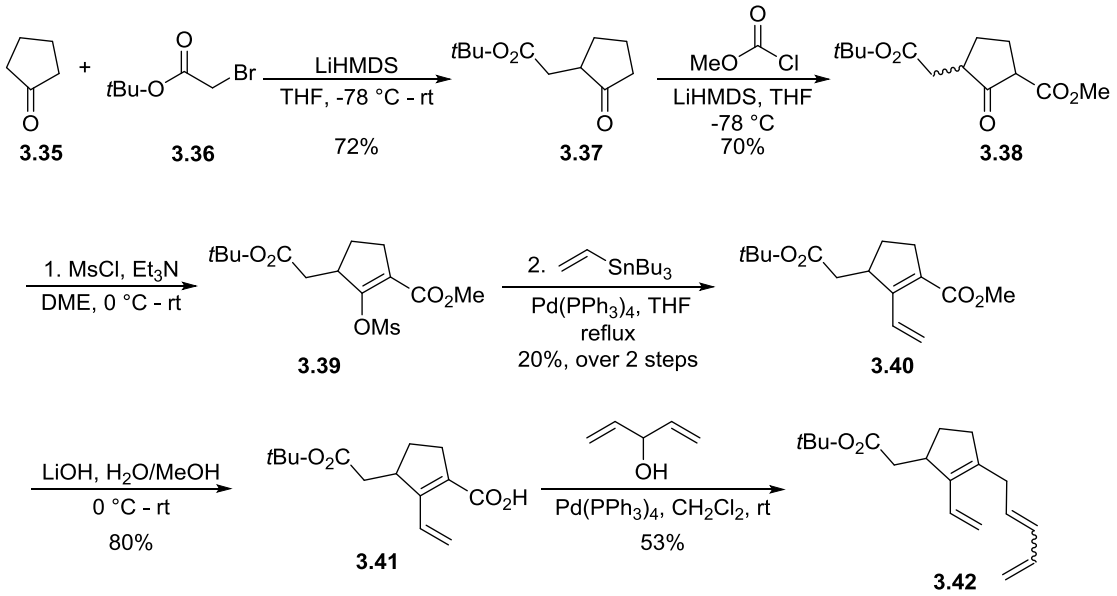
3.30

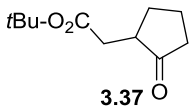
(1*R*,2*R*,3a*S*,7a*S*)-1-vinyl-2,3,3a,4,5,6,7,7a-octahydro-1H-cyclopenta[a]pentalen-2-ol, 3.30

To a solution of tetraene **3.29** (2.5 mg, 0.013 mmol) in 1,2-dichloroethane (0.1 mL) were added $[RhCl(CO)_2]_2$ (1.0 mg, 0.0026 mmol) and $AgSbF_6$ (0.45 mg, 0.0013 mmol) before purging thoroughly with CO. A CO filled balloon was used to maintain a constant CO atmosphere and the reaction was heated to 80 °C using an oil bath for 14

hours. The reaction was then cooled to -40 °C and MeOH (0.1 mL) and triphenylphosphine (0.34 mg, 0.0013 mmol) were added prior to the addition of $NaBH_4$ (1.0 mg, 0.027 mmol). After 20 minutes, the reaction was poured over water and extracted 2x with CH_2Cl_2. The aqueous layer was then acidified to a pH ~ 3 by the addition of a 10% aqueous HCl after which two more extractions were done using CH_2Cl_2. The combined organic layers were then washed with brine, dried using Na_2SO_4 and concentrated to yield tricycle **3.30** and other isomerized products. Tricycle **3.30** was not fully characterized due to isomerization.

4.4 Synthesis of Tetraene 3.42 in the Real System





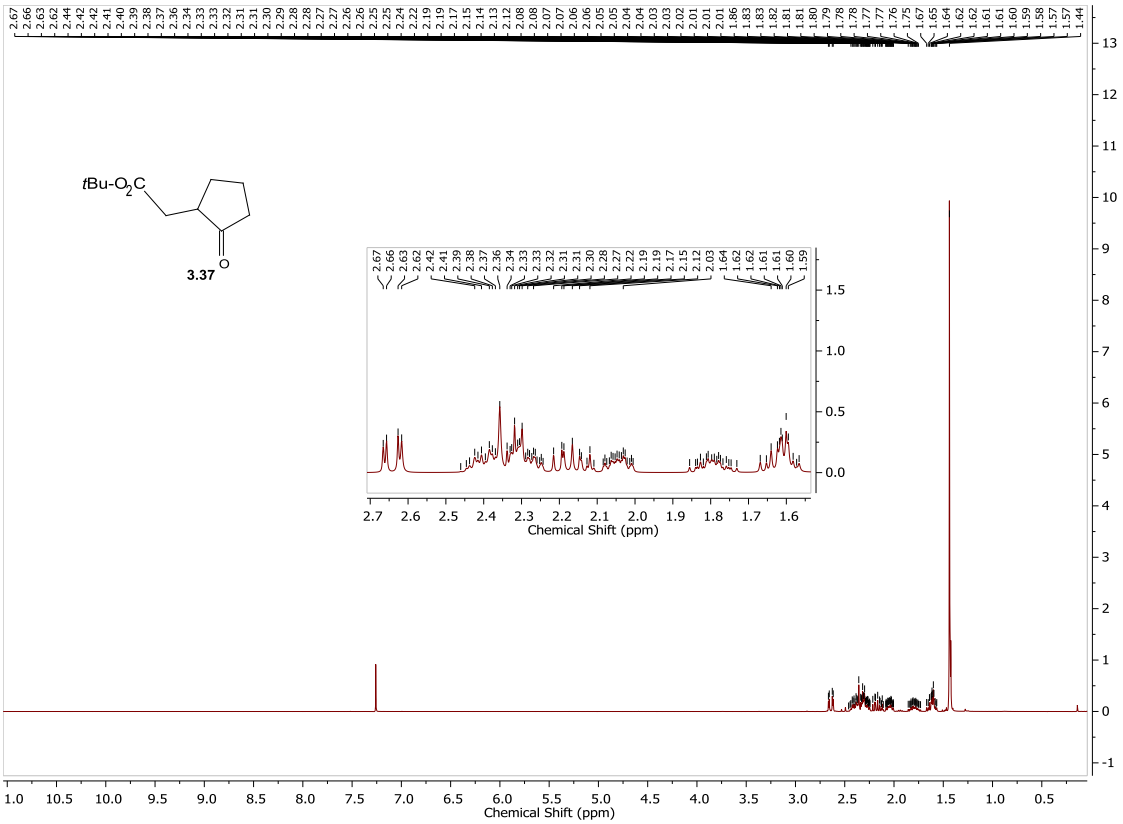
***tert*-butyl 2-(2-oxocyclopentyl)acetate, 3.37**

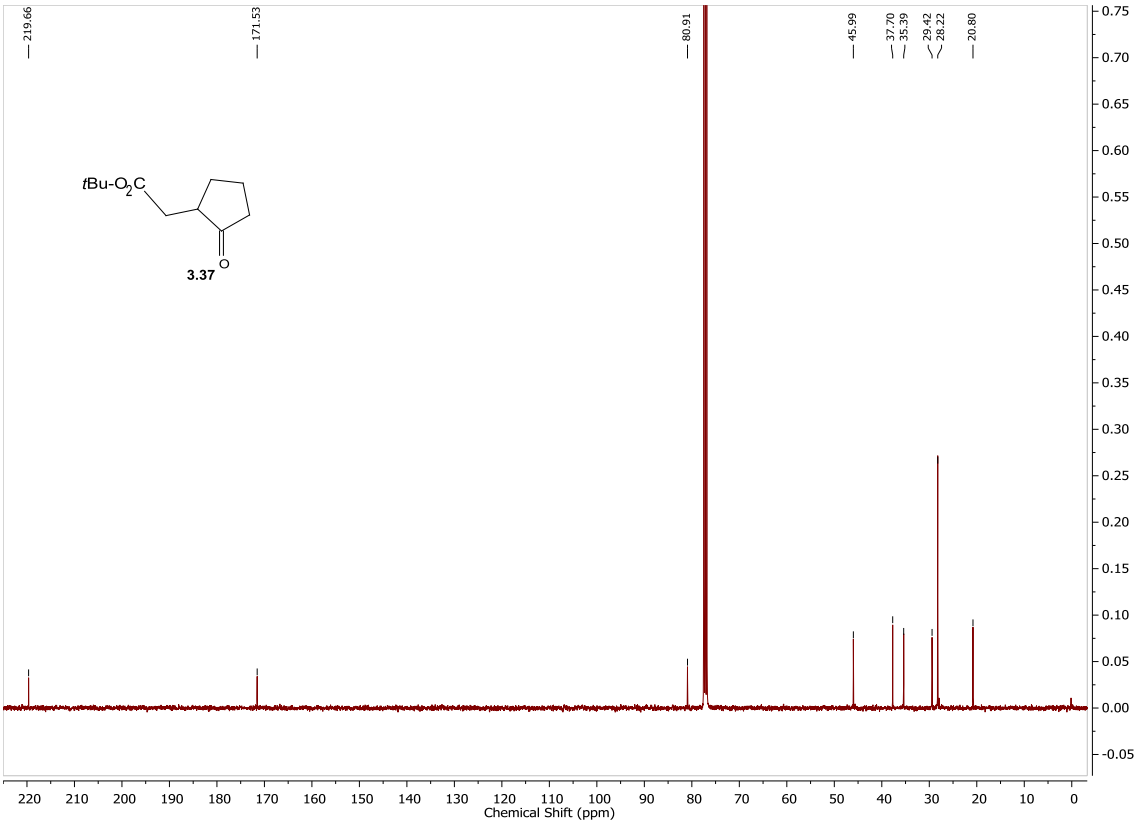
To a stirred solution of LiHMDS (4.7 g, 28 mmol) in THF (170 mL) at -78 °C, was added slowly a solution of cyclopentanone **3.35** (2.5 mL, 28 mmol) in THF (30 mL). After an hour the reaction temperature was raised to -20 °C gradually over 30 minutes. The reaction temperature was lowered to -78 °C, and a solution of *tert*-butyl bromoacetate (5.0 mL, 34 mmol) in THF (30 mL) was added slowly and the reaction was left to warm gradually to room temperature. After stirring overnight, the reaction was quenched with saturated NH_4Cl solution, and extracted 2x with diethyl ether. The combined organic layers were washed with water and brine subsequently, dried using Na_2SO_4 and concentrated. Purification via silica gel chromatography (95:5, hexanes/acetone) yielded ester **3.37** (4.0 g, 72% yield) as a colorless oil. R_f = 0.43 (90:10, hexanes/acetone).

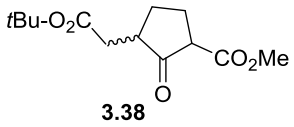
^{1}H NMR (400 MHz, $CDCl_3$) δ 2.64 (dd, J = 15.8, 3.7 Hz, 1H), 2.46 – 2.24 (m, 4H), 2.22 – 2.11 (m, 1H), 2.04 (dddt, J_d = 12.4, 8.4, 6.3, J_t = 1.8 Hz, 1H), 1.79 (dddt, J = 11.7, 11.1, 8.2, 6.3 Hz, 1H), 1.67 – 1.57 (m, 1H), 1.44 (s, 9H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 219.6, 171.5, 80.9, 45.9, 37.7, 35.3, 29.4, 28.2 (3C), 20.8 ppm.

HRMS (ESI) calcd. for $[C_{11}H_{18}O_3+Na]^+$: 221.1148, found: 221.1149.


tBu-O2C
O
3.37
Chemical Shift (ppm)
Chemical Shift (ppm)





3.38

Methyl 3-(2-(*tert*-butoxy)-2-oxoxyxlopentane-1-carboxylate, 3.38

To a stirred solution of LiHMDS (4.2 g, 25 mmol) in THF (70 mL) at -78 °C, was added slowly a solution of *tert*-butyl 2-(2-oxocyclopentyl)acetate **3.37** (2.5 g, 13 mmol) in THF (26 mL). After an hour stirring a solution of methyl chloroformate (1.9 mL, 25 mmol) in THF (26 mL) was added slowly. After stirring for four hours at the same temperature the reaction turned from dark yellow to bright orange. The reaction was quenched with a saturated NH_4Cl solution, and extracted 3x with CH_2Cl_2. The organic

layers were washed with water and brine subsequently, dried using Na_2SO_4 and concentrated. Purification via silica gel chromatography (90:10, hexanes/acetone) yielded diester **3.38** (2.5 g, 70%) as a rusty pink oil. Two isomers are produced, diastereomers A and B. The diastereomeric ratio is 2.5:1.0 with diastereomer A eluting early.

Diastereomer A:

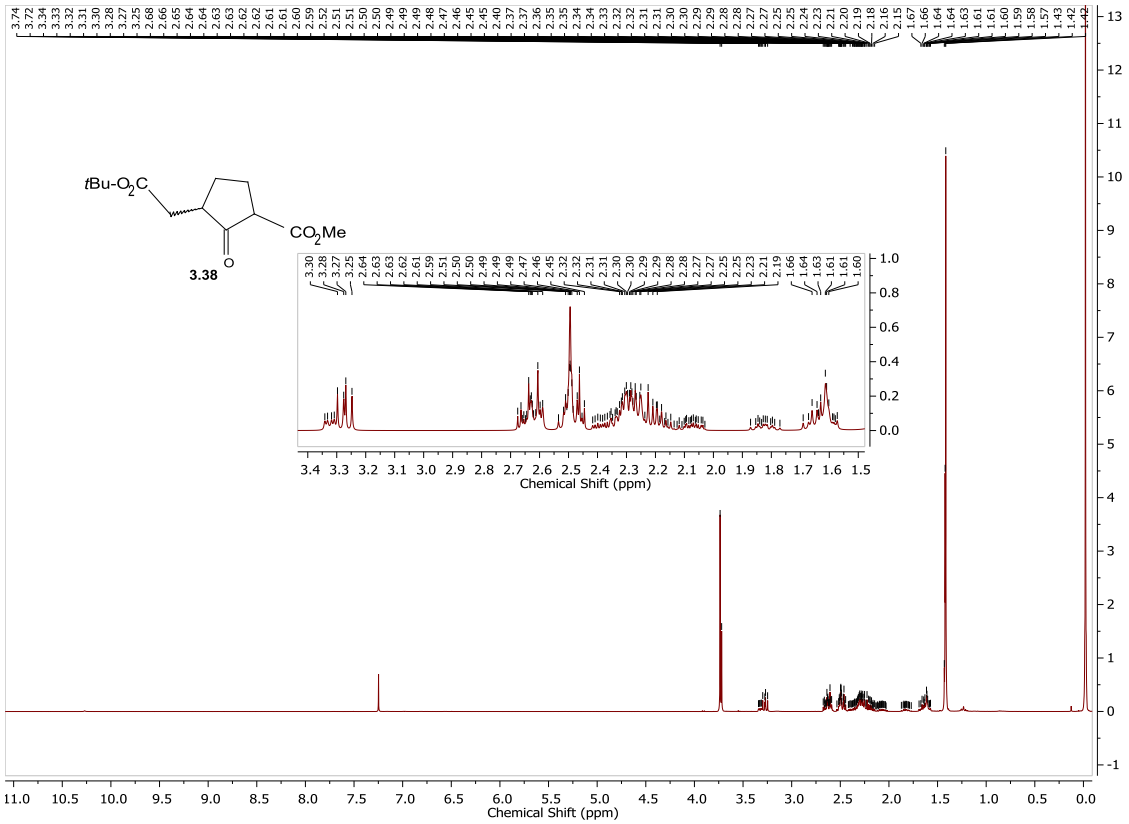
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.73 (s, 3H), 3.34 (dd, J = 9.3, 3.8 Hz, 1H), 2.68 – 2.59 (m, 1H), 2.53 – 2.45 (m, 1H), 2.37 – 2.15 (m, 4H), 1.69 – 1.57 (m, 1H), 1.43 (s, 9H) ppm. R_f = 0.32 (90:10, hexanes/acetone).

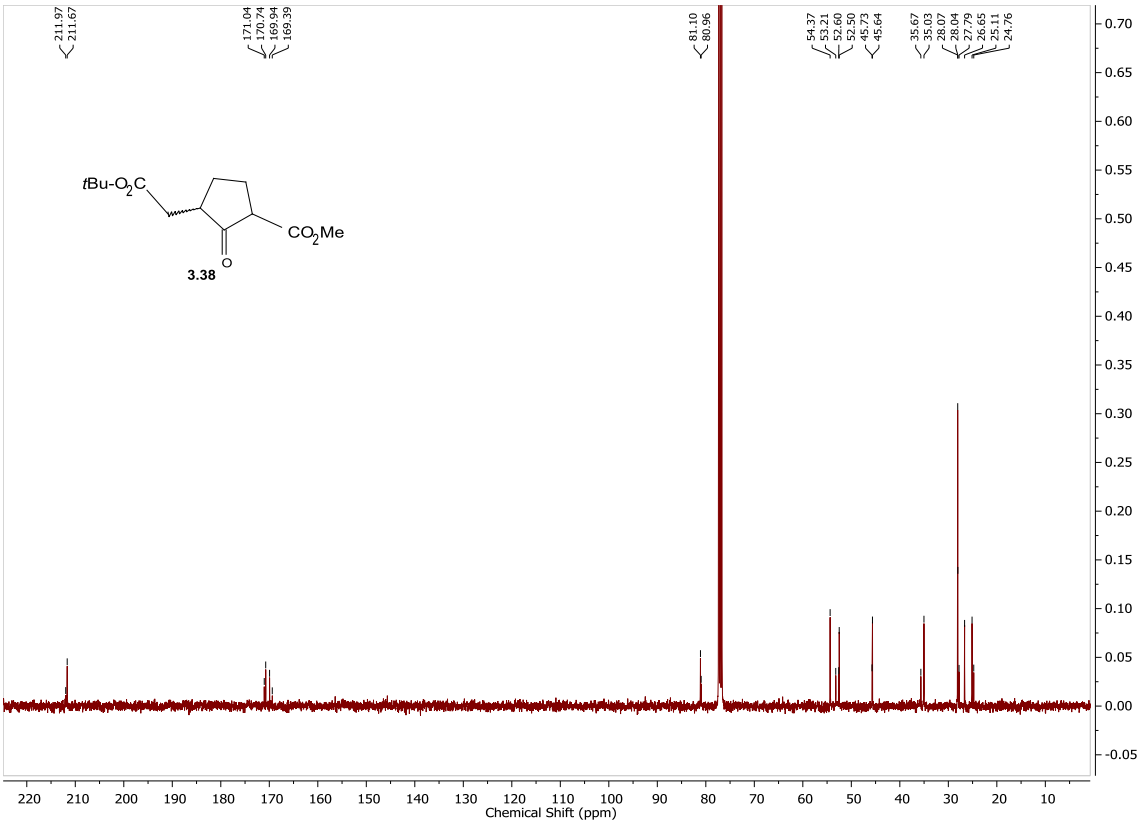
Diastereomer B:

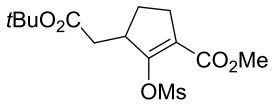
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.75 (s, 3H), 3.28 (dd, J = 11.5, 8.5 Hz, 1H), 2.68 – 2.59 (m, 1H), 2.53 – 2.45 (m, 2H), 2.42 – 2.36 (m, 2H), 2.10 – 2.02 (m, 1H), 1.82 (dtd, J_d = 12.7, J_t = 10.3, J_d = 7.2 Hz, 1H), 1.43 (s, 9H) ppm. R_f = 0.27 (90:10, hexanes/acetone).

^{13}C NMR (100 MHz, $CDCl_3$) δ 211.7 (2C), 1.71.0, 170.7, 169.9, 169.4, 81.1, 81.0, 54.4, 53.2, 52.6, 52.5, 45.7, 45.6, 35.7, 35.0, 28.1 (3C), 28.0 (3C), 27.8, 26.7, 25.1, 24.7 ppm.

HRMS (ESI) calcd. for $[C_{13}H_{20}O_5+H]^+$: 257.1384, found: 257.1389.


tBu-O2C
CO2Me
O
3.38
Chemical Shift (ppm)
Chemical Shift (ppm)



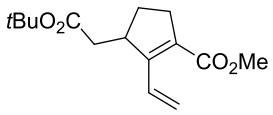


3.39

Methyl 3-(2-*tert*-butoxy)-2-oxoethyl)-2-((methylsulfonyl)oxy)cyclopent-1-ene-1-carboxylate, 3.39

To a mixture of diester **3.38** (57 mg, 0.22 mmol) in DME (2.2 mL) at 0 °C were slowly added triethylamine (0.15 mL, 1.1 mmol) and mesyl chloride (0.04 mL, 0.57 mmol). The reaction mixture was then allowed to warm to room temperature for 14 h, diluted with diethyl ether, and washed with water. The aqueous layer was back extracted 2x with diethyl ether, and the organic layers were combined, washed with water and a

saturated NaCl solution. The solution was dried using Na_2SO_4 and concentrated to yield mesylate **3.39** as a brown oil. This β-mesyloxyenone decomposes on standing neat at room temperature for several hours. It was used in the subsequent Stille coupling without further purification immediately after formation. R_f = 0.62 (70:30, hexanes/EtOAc). Mesylate **3.39** was not fully characterized as a result of the formation of another unknown byproduct.



3.40

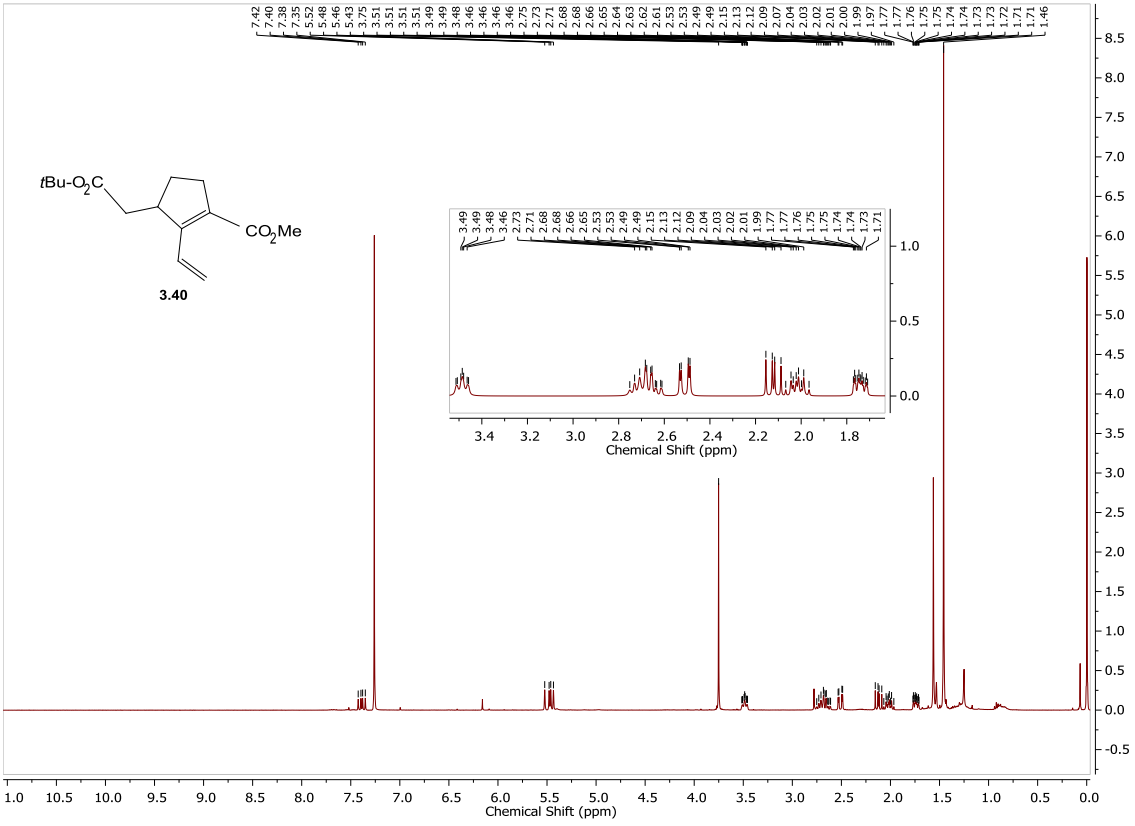
Methyl 3-(2-(*tert*-butoxy)-2-oxoethyl)-2-vinylcyclopent-1-ene-1-carboxylate, 3.40

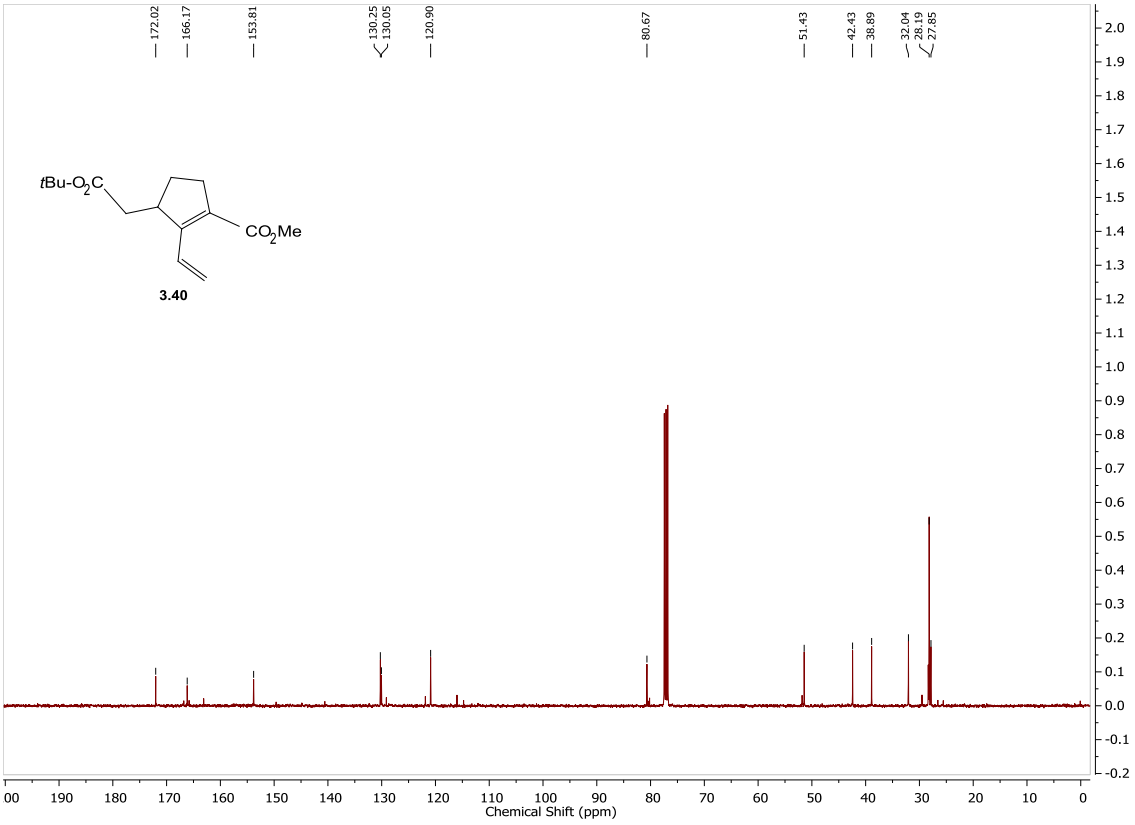
To a solution of LiBr (661 mg, 7.6 mmol) and $Pd(PPh_3)_4$ (293 mg, 5 mol %) in THF (30 mL) was added a solution of mesylate **3.39** (1.6 g, 5.0 mmol) and vinyltributylstannane (2.9 mL, 9.9 mmol) in THF (20 mL) under an atmosphere of N_2. The solution was refluxed for 48 hours, cooled to room temperature, diluted with CH_2Cl_2 and washed with water. The aqueous layer was back extracted 2x with CH_2Cl_2, and the combined organic layers were washed with 10% NH_4OH aqueous solution (2x50 mL), water and saturated aqueous NaCl. The solution was dried using Na_2SO_4 and concentrated before purification via silica gel chromatography (98:2, hexanes/EtOAc) to give ester **3.40** (232 mg, 20% (over 2 steps)) as a yellow oil. R_f = 0.58 (90:10, hexanes/EtOAc).

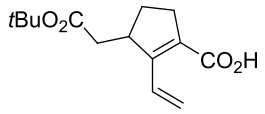
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (dd, J = 17.9, 11.0 Hz, 1H), 5.52 – 5.43 (m, 2H), 3.75 (s, 3H), 3.51 – 3.46 (m, 1H), 2.75 – 2.61 (m, 2H), 2.50 (dd, J = 15.3, 3.0 Hz, 1H), 2.11 (dd, J = 15.4, 11.1 Hz, 1H), 2.01 (dq, J_d = 13.2, J_q = 9.3 Hz, 1H), 1.73 (ddt, J_d = 13.3, 7.6, J_t = 2.0 Hz, 1H), 1.46 (s, 9H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 166.2, 153.8, 130.3, 130.1, 120.9, 80.7, 51.4, 42.4, 38.9, 32.0, 28.2 (3C), 27.9 ppm.

HRMS (APPI) calcd. for $[C_{15}H_{22}O_4+Na]^+$: 289.1410, found: 289.1410.







3.41

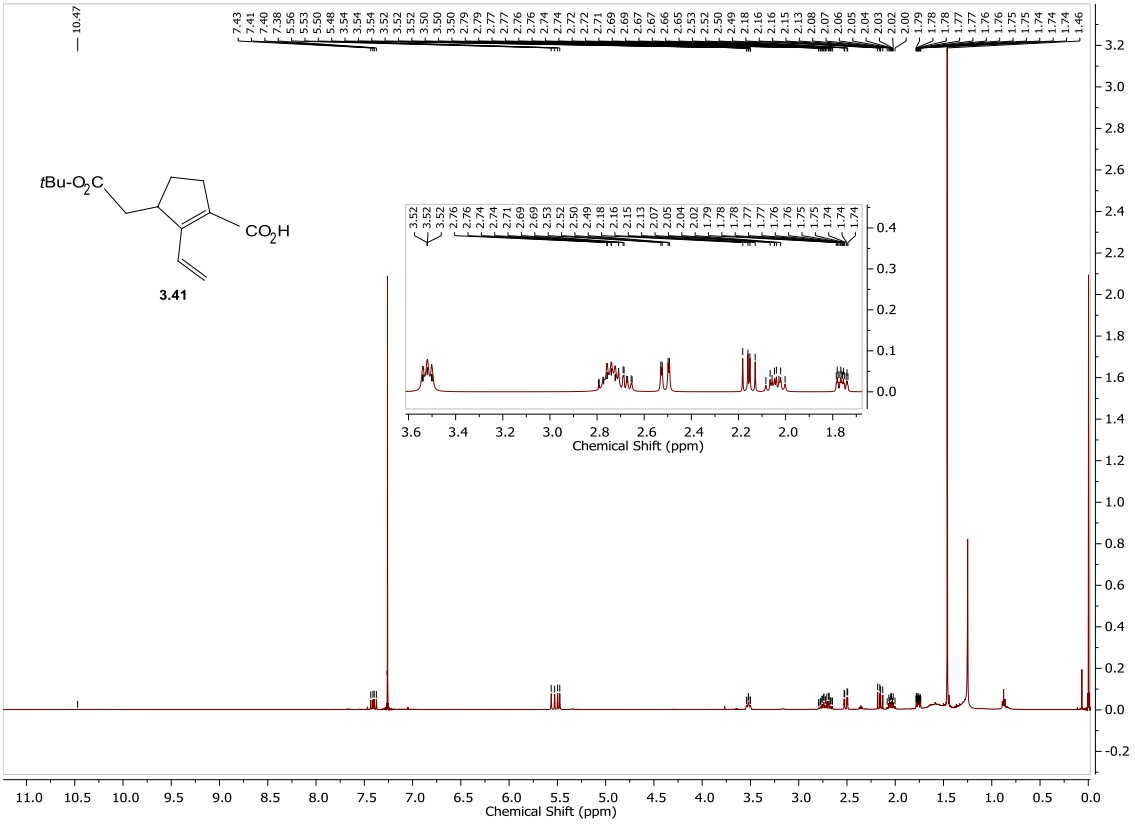
3-(2-(*tert*-butoxy)-2-oxyethy)-2-vinylcyclopent-1-ene-1-carboxylic acid, 3.41

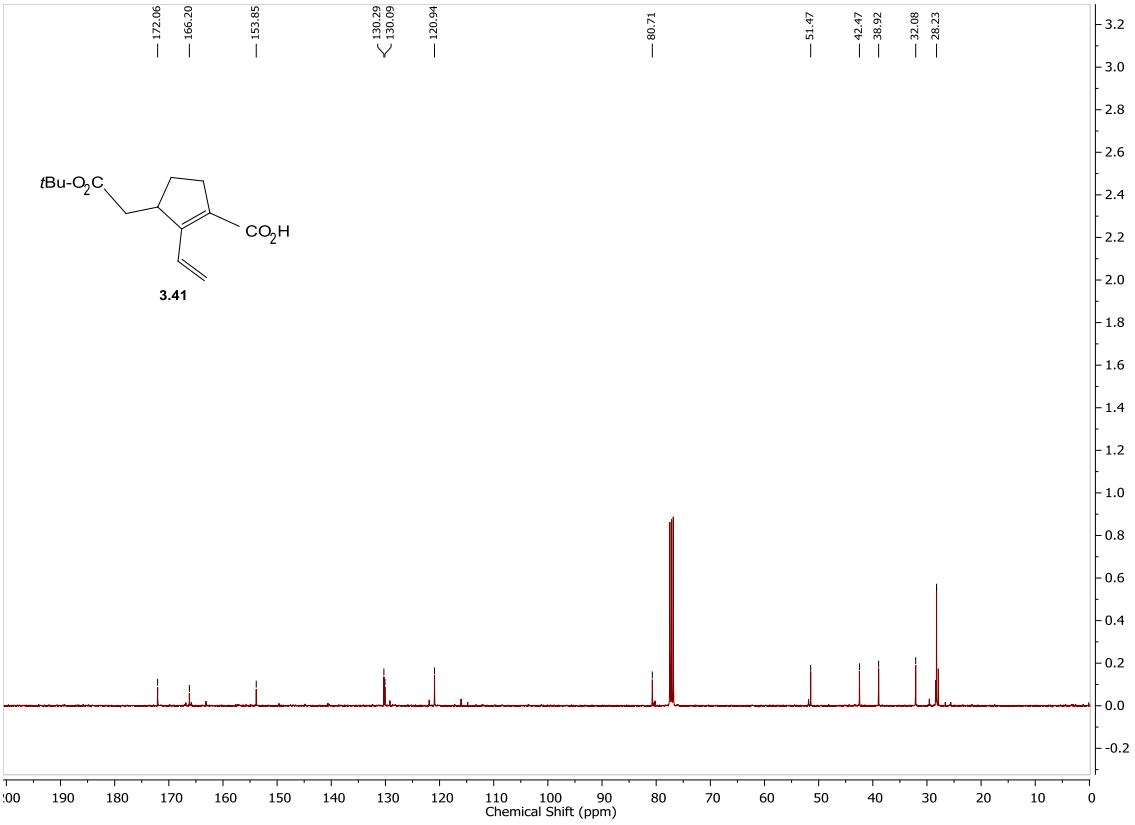
LiOH (0.05 mL, 10% in 1:1, MeOH:H_2O) was added to dienoate **3.40** (3.2 mg, 0.013 mmol) in THF (0.1 mL) at 0 °C. The mixture was left to warm to room temperature for 12 hours and turned from colorless to brown. The mixture was acidified with 10% aqueous HCl until pH ~ 2, extracted 3x with diethyl ether, dried over Na_2SO_4, and concentrated to give dienoic acid **3.41** (2.4 mg, 80%) as an off-white solid. R_f = 0.27 (70:30, hexanes/EtOAc, large streak).

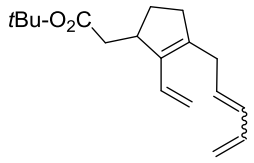
^{1}H NMR (500 MHz, $CDCl_3$) δ 10.47 (bs, 1H), 7.40 (dd, J = 17.8, 11.0 Hz, 1H), 5.56 – 5.48 (m, 2H), 3.50 – 3.54 (m, 1H), 2.79 – 2.65 (m, 2H), 2.51 (dd, J = 15.4, 2.9 Hz, 1H), 2.16 (dd, J = 15.4, 11.1 Hz, 1H), 2.04 (dq, J_d = 13.1, J_q = 9.2 Hz, 1H), 1.76 (ddt, J_d = 13.0, 7.6, J_t = 2.0 Hz, 1H), 1.46 (s, 9H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 166.2, 153.9, 130.3, 130.1, 120.9, 80.7, 51.5, 42.5, 38.9, 32.1, 28.2 (3C) ppm.

HRMS (ESI) calcd. for $[C_{14}H_{20}O_4\text{-}H]^-$: 251.1283, found: 251.1283.







3.42

(6*E*/*Z*,8*E*)-methyl 6-allylideneundeca-8,10-dienoate, 3.42

A microwave vial with dienoic acid **3.41** (2.4 mg, 0.0097 mmol) and 1,4-pentadien-3-ol **3.4** (1.2 µL, 0.012 mmol) in CH_2Cl_2 (0.1 M) was capped with a septum, purged with N_2, tetrakis(triphenylphosphine) palladium (1.2 mg, 10 mol %) was added, and the vial was sealed and purged with N_2. The mixture was left at room temperature under a balloon of N_2 for 48 hours. The solution was concentrated and purified via silica

gel chromatography (98:2, hexanes/EtOAc) to yield tetraene **3.42** (1.4 mg, 53%) as a yellow oil. Two isomers are produced, diastereomers A and B. The diastereomeric ratio is 3.0:1.0 with diastereomer A eluting early.

Diastereomer A (major):

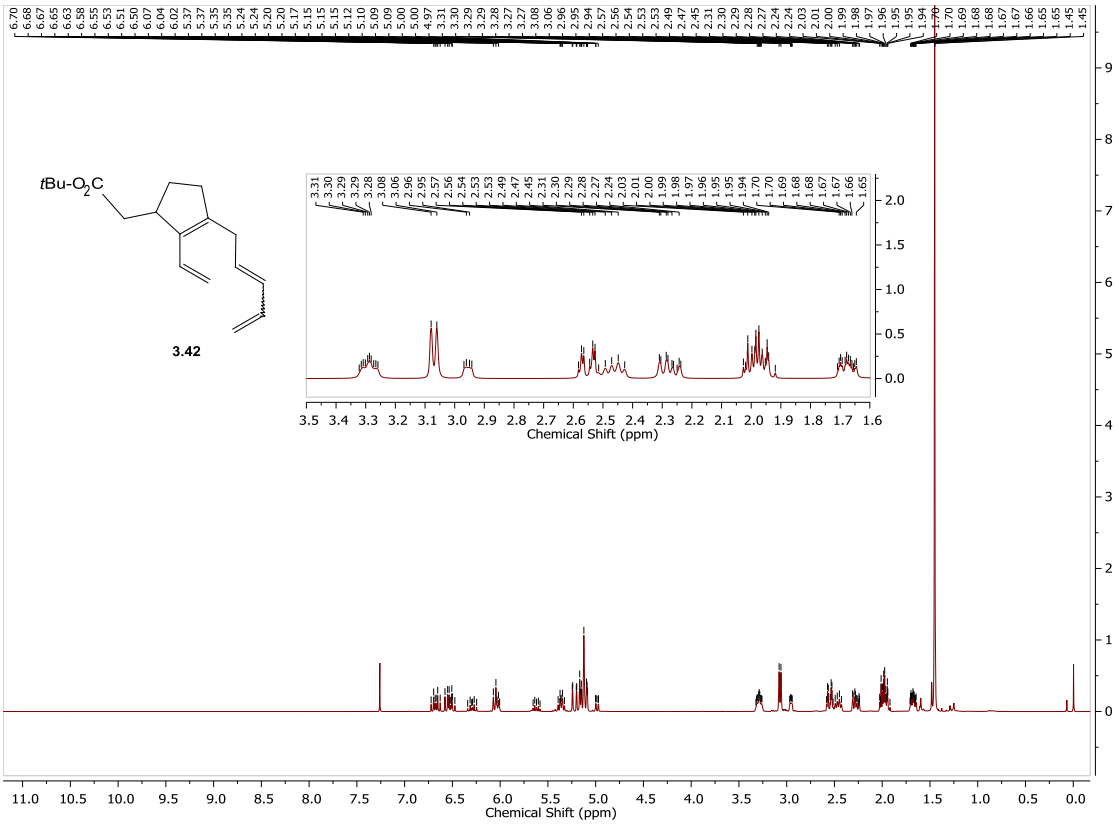
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.72 – 6.63 (m, 1H), 6.58 – 6.47 (m, 1H), 6.07 – 6.01 (m, 1H), 5.39 – 5.33 (m, 1H), 5.24 – 5.20 (m, 1H), 5.17 – 5.09 (m, 3H), 3.32 – 3.26 (m, 1H), 3.07 (d, J = 7.7 Hz, 2H), 2.58 – 2.51 (m, 1H), 2.49 – 2.43 (m, 1H), 2.31 – 2.24 (m, 1H), 2.03 – 1.92 (m, 2H), 1.71 – 1.65 (m, 1H), 1.45 (s, 9H) ppm. R_f = 0.67 (90:10, hexanes/EtOAc).

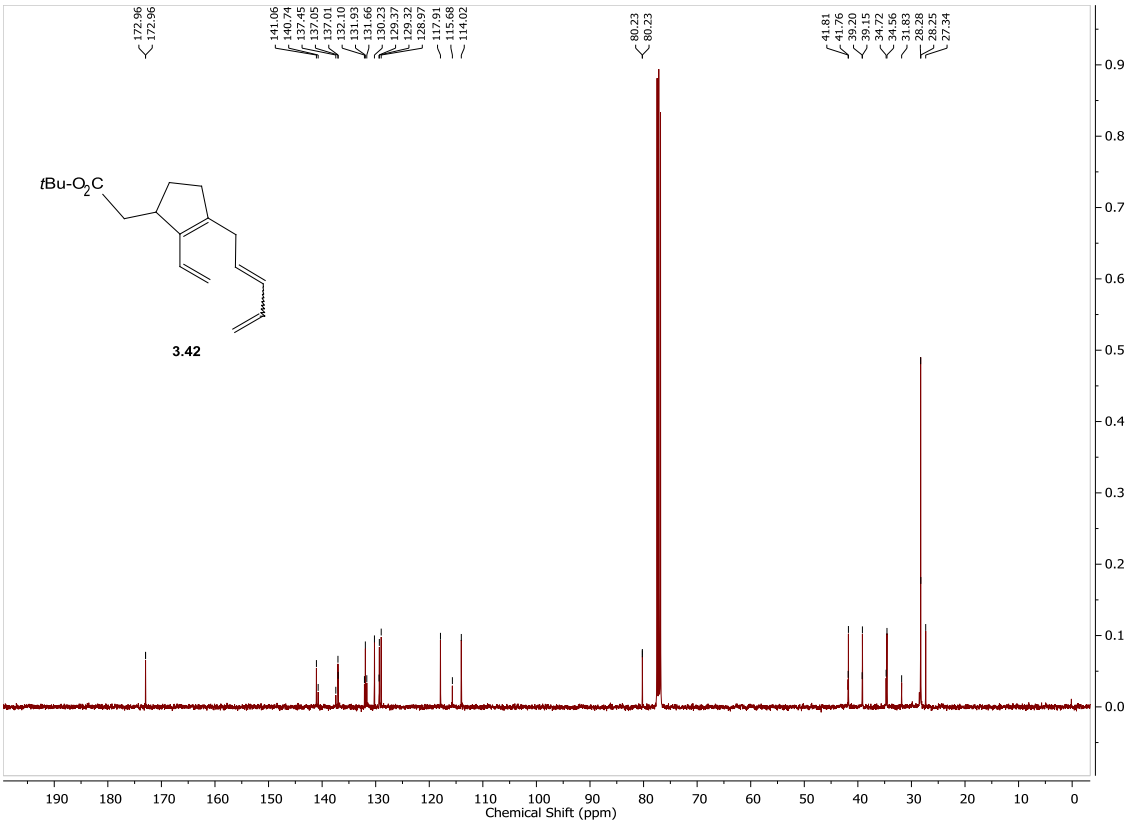
Diastereomer B (minor):

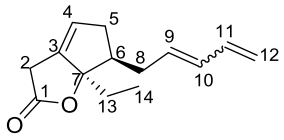
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.72 – 6.63 (m, 1H), 6.58 – 6.47 (m, 1H), 6.29 (dt, J_d = 17.0, J_t = 10.3 Hz, 1H), 6.07 – 6.01 (m, 1H), 5.65 – 5.58 (m, 1H), 5.17 – 5.09 (m, 1H), 4.99 (d, J = 10.4, 2H), 3.32 – 3.26 (m, 1H), 2.96 (dd, J = 7.5, 3.2 Hz, 2H), 2.58 – 2.51 (m, 1H), 2.49 – 2.43 (m, 1H), 2.31 – 2.24 (m, 1H), 2.03 – 1.92 (m, 2H), 1.71 – 1.65 (m, 1H), 1.45 (s, 9H) ppm. R_f = 0.60 (90:10, hexanes/EtOAc).

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9 (2C), 141.2, 140.7, 137.5, 137.1, 137.0, 132.1, 131.9, 131.7, 130.2, 129.4, 129.3, 128.9, 117.9 (2C), 115.7, 114.0, 80.2 (2C), 41.8 (2C), 39.2 (2C), 34.7, 34.6 (2C), 31.8, 28.3 (6C), 27.3 (2C) ppm.

HRMS (ESI) calcd. for $[C_{18}H_{26}O_2+H]^+$: 275.2006, found: 275.2003.


tBu-O2C
3.42
Chemical Shift (ppm)
Chemical Shift (ppm)





3.45

6a-ethyl-6-(penta-2,4-dien-1-yl)-3,5,6,6a-tetrahydro-2H-cyclopenta[b]furan-2-one, 3.45

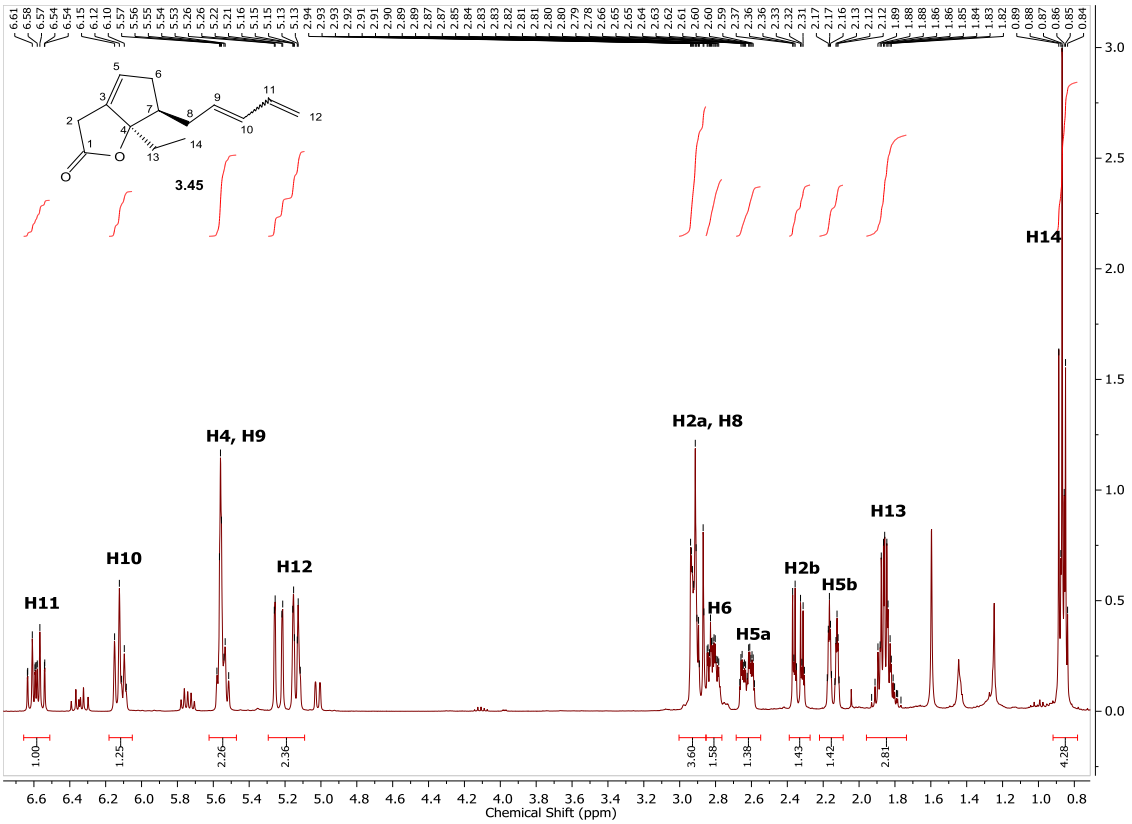
To a solution of tetraene **3.42** (43 mg, 0.16 mmol) in 1,2-dichloroethane (2.1 mL) were added $[RhCl(CO)_2]_2$ (8.3 mg, 0.021 mmol) and $AgSbF_6$ (4.9 mg, 0.016 mmol) before purging thoroughly with CO. A CO filled balloon was used to maintain a constant CO atmosphere and the reaction was left at room temperature for 14 hours. The solvent

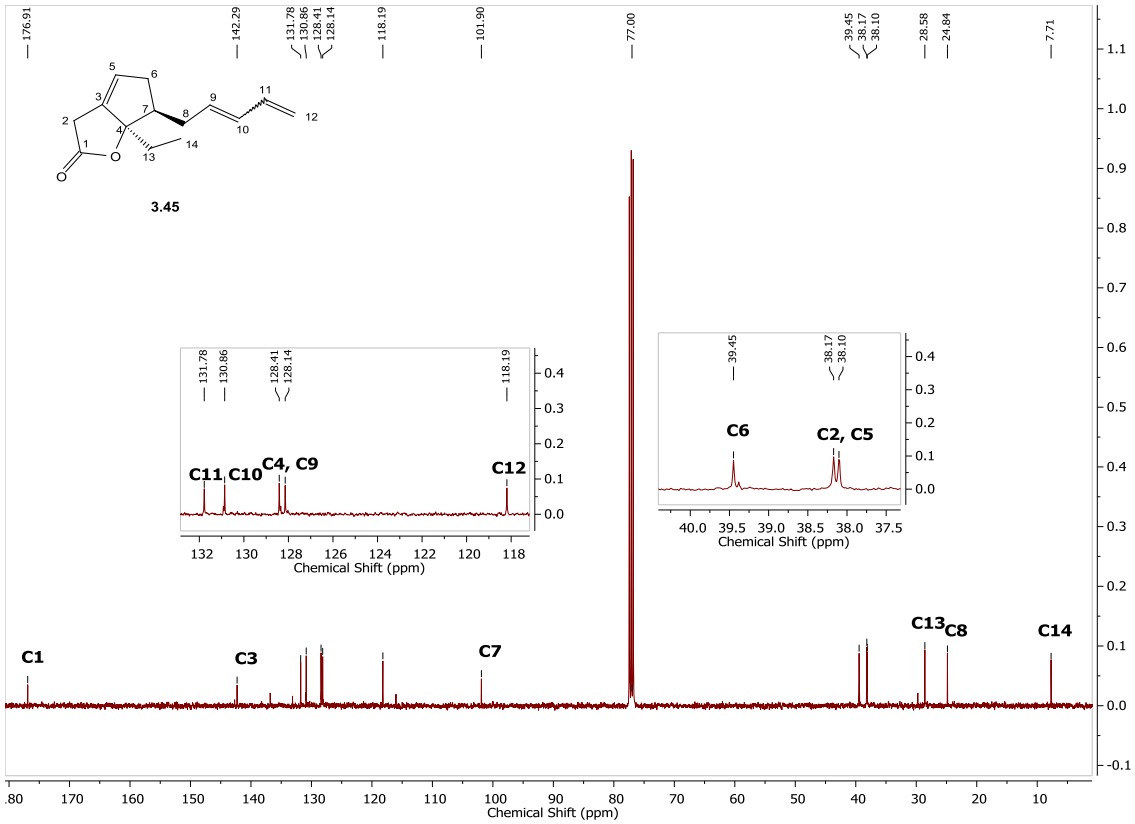
was concentrated and the crude was purified via silica gel chromatography (80:20, hexanes/EtOAc) to yield compound **3.45** (8.8 mg, 24%) as a yellow oil. R_f = 0.36 (80:20, hexanes/EtOAc). Two isomers are produced, diastereomers A and B. The diastereomeric ratio is 4.0:1.0 with diastereomer B eluting early. Only isomer A was analyzed.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.59 (dt, J_d = 16.6, J_t = 10.6 Hz, 1H), 6.15 – 6.08 (m, 1H), 5.58 – 5.51 (m, 2H), 5.26 – 5.12 (m, 2H), 2.96 – 2.85 (m, 3H), 2.82 (dddd, J = 10.4, 7.8, 5.5, 2.1 Hz, 1H), 2.66 – 2.58 (m, 1H), 2.37 – 2.30 (m, 1H), 2.18 – 2.11 (m, 1H), 1.93 – 1.77 (m, 2H), 0.89 – 0.84 (m, 3H) ppm.

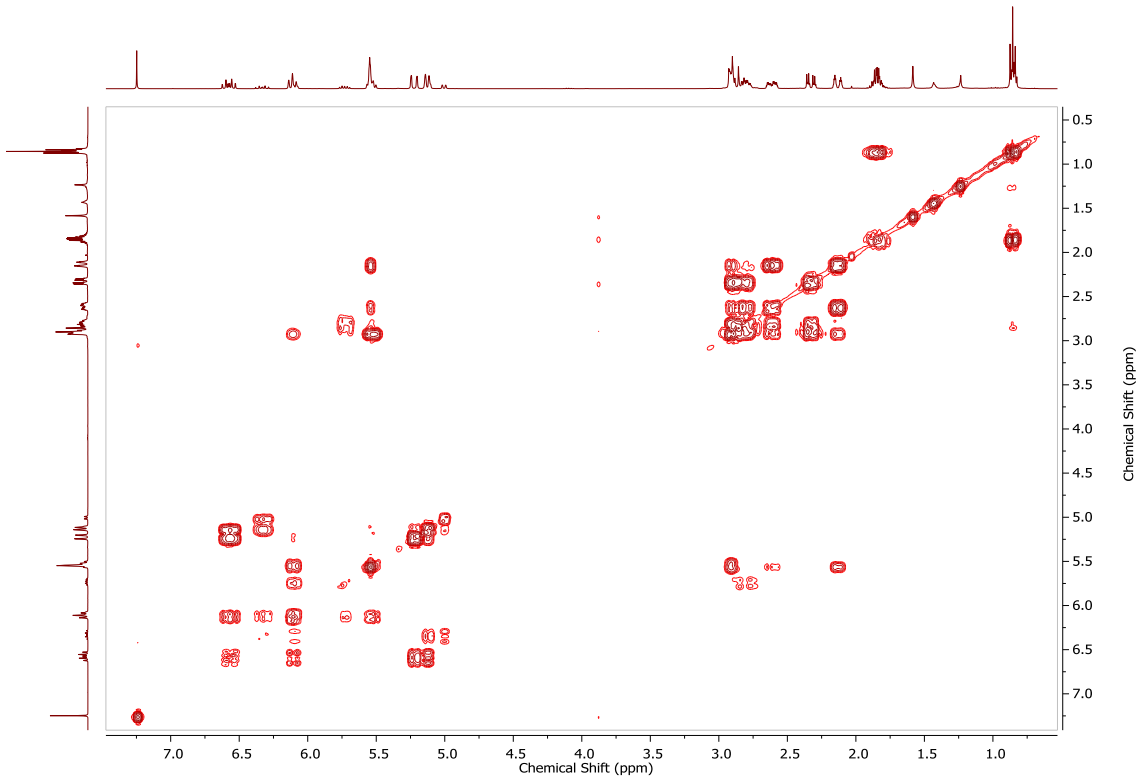
^{13}C NMR (101 MHz, $CDCl_3$) δ 176.9, 142.3, 131.8, 130.9, 128.4, 128.1, 118.2, 101.9, 39.5, 38.2, 38.1, 28.6, 24.8, 7.7 ppm.

HRMS (ESI) calcd. for $[C_{14}H_{18}O_2+H]^+$: 219.1385, found: 219.1380.

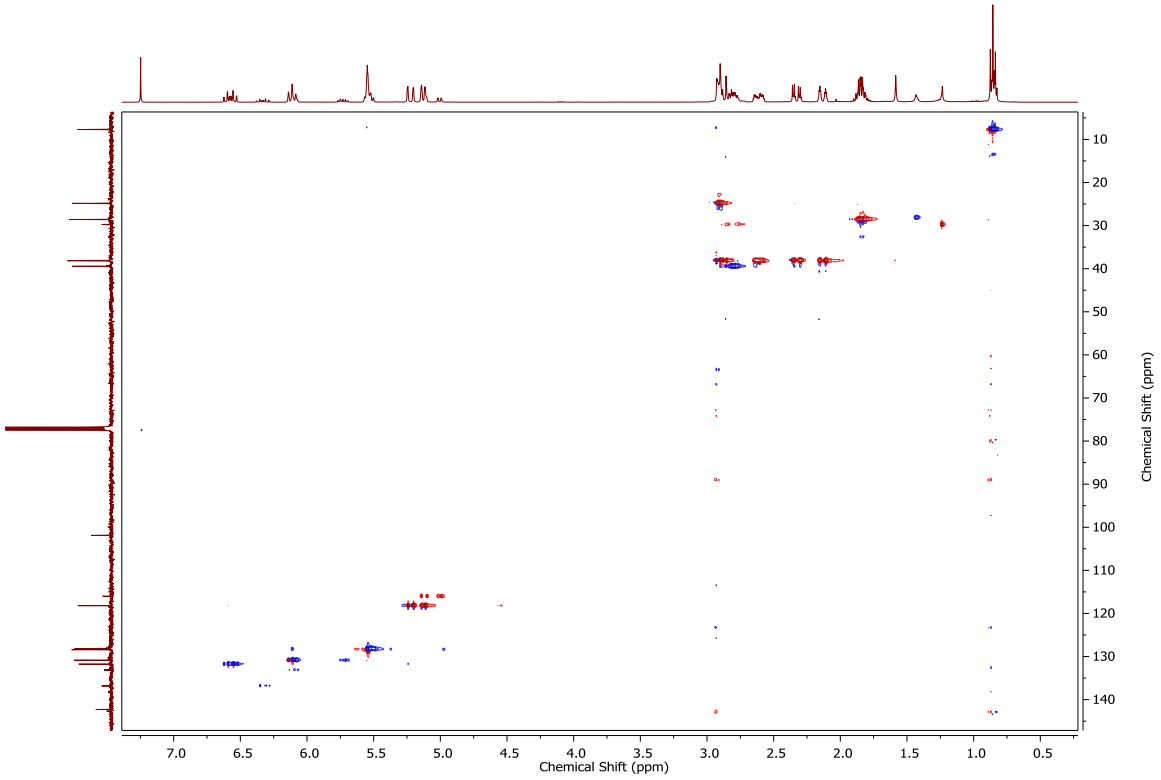

3.45
H11
H10
H4, H9
H12
H2a, H8
H6
H5a
H2b
H5b
H13
H14
Chemical Shift (ppm)


176.91
142.29
131.78
130.86
128.41
128.14
118.19
101.90
77.00
39.45
38.17
38.10
28.58
24.84
7.71
3.45
C1
C3
C7
C13
C8
C14
C11
C10
C4, C9
C12
C6
C2, C5
Chemical Shift (ppm)

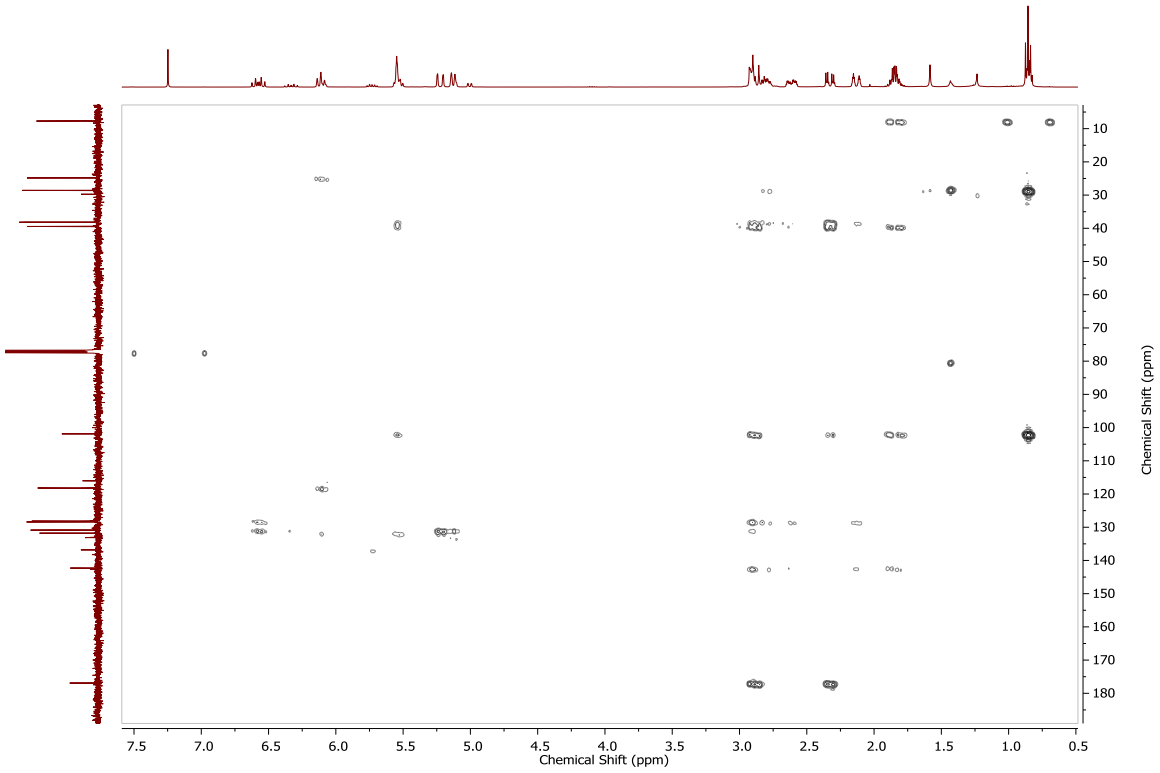
COSY for Structure 3.45

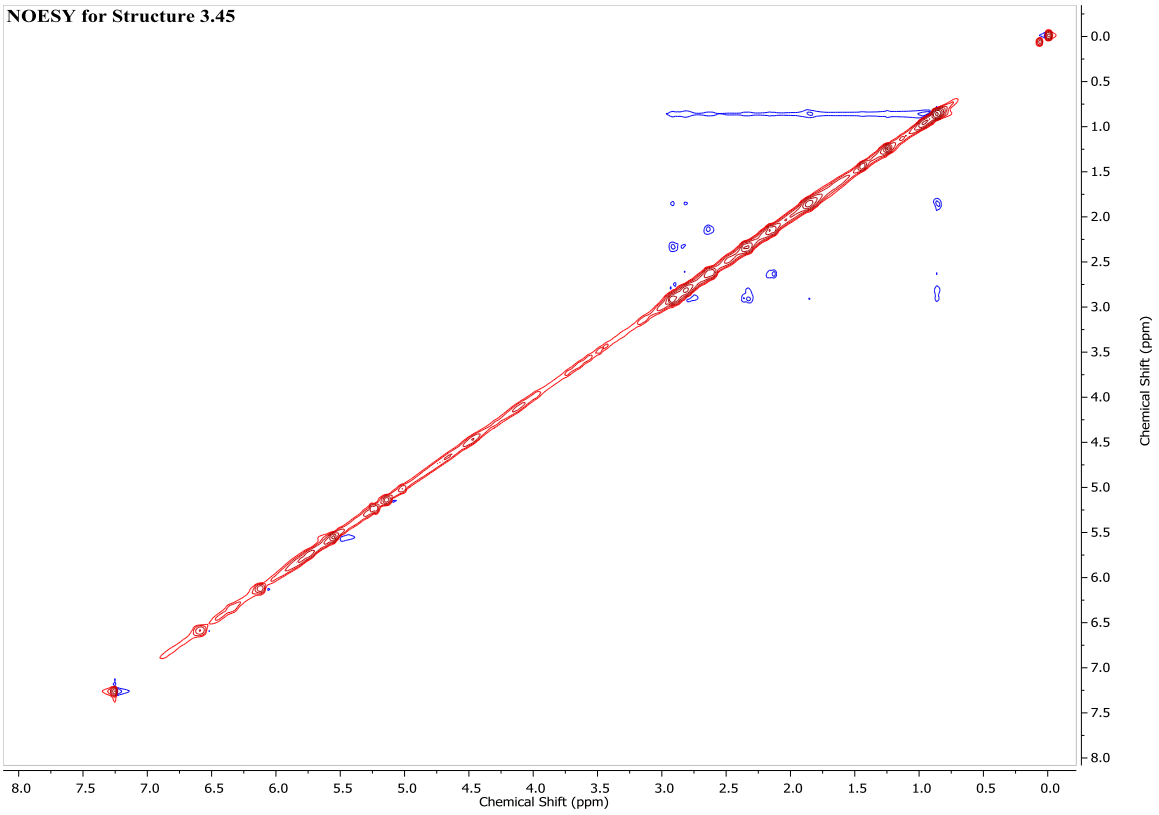


HSQC for Structure 3.45



HMBC for Structure 3.45




NOESY for Structure 3.45
Chemical Shift (ppm)
Chemical Shift (ppm)

5. References

1. Lutsep, H. L.; Clark, W. M. *Formulary* **1997**, *32*, 1040–1047.

2. Mozaffarian, D.; Benjamin, E. J.; Go, A. S.; Arnett, D. K.; Blaha, M. J.; Cushman, M.; Das, S. R.; Ferranti, S. de; Després, J.-P.; Fullerton, H. J.; Howard, V. J.; Huffman, M. D.; Isasi, C. R.; Jiménez, M. C.; Judd, S. E.; Kissela, B. M.; Lichtman, J. H.; Lisabeth, L. D.; Liu, S.; Mackey, R. H.; Magid, D. J.; McGuire, D. K.; Mohler, E. R.; Moy, C. S.; Muntner, P.; Mussolino, M. E.; Nasir, K.; Neumar, R. W.; Nichol, G.; Palaniappan, L.; Pandey, D. K.; Reeves, M. J.; Rodriguez, C. J.; Rosamond, W.; Sorlie, P. D.; Stein, J.; Towfighi, A.; Turan, T. N.; Virani, S. S.; Woo, D.; Yeh, R. W.; Turner, M. B. *Circulation* **2015**, CIR.0000000000000350.

3. He, Y.; Li, Y.; Chen, Y.; Feng, L.; Nie, Z. *Nutr. Metab. Cardiovasc. Dis. NMCD* **2014**, *24*, 1158–1165.

4. Moser, M.; Wright, J. T.; Victor, R. G.; Handler, J. *J. Clin. Hypertens.* **2008**, *10*, 390–397.

5. Sims, N. R.; Muyderman, H. *Biochim. Biophys. Acta* **2010**, *1802*, 80–91.

6. Plum F *JAMA* **2001**, *285*, 1760–1761.

7. Cui Y; Takamatsu H; Kakiuchi T; Ohba H; Kataoka Y; Yokoyama C; Onoe H; Watanabe Y; Hosoya T; Suzuki M; Noyori R; Tsukada H; Watanabe Y *Stroke J. Cereb. Circ.* **2006**, *37*, 2830–2836.

8. Suzuki, M.; Noyori, R.; Långström, B.; Watanabe, Y. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 1053–1070.

9. Mazighi, M.; Chaudhry, S. A.; Ribo, M.; Khatri, P.; Skoloudik, D.; Mokin, M.; Labreuche, J.; Meseguer, E.; Yeatts, S. D.; Siddiqui, A. H.; Broderick, J.; Molina, C. A.; Qureshi, A. I.; Amarenco, P. *Circulation* **2013**, *127*, 1980–1985.

10. Carden, D. L.; Granger, D. N. *J. Pathol.* **2000**, *190*, 255–266.

11. Karasawa, Y.; Hitomi, T.; Komiyama, H.; Isobe, Y.; Kobayashi, T.; Yoshida, S.; Nakaike, S.; Araki, H. *Eur. J. Pharmacol.* **2002**, *449*, 127–133.

12. Matsuda, S.; Wen, T.-C.; Karasawa, Y.; Araki, H.; Otsuka, H.; Ishihara, K.; Sakanaka, M. *Brain Res.* **1997**, *769*, 321–328.

13. Yamashita, K.; Kataoka, Y.; N.-Nakashima, M.; S.-Yamashita, Y.; Tanabe, H.; Araki, H.; Niwa, M.; Taniyama, K. *Jpn. J. Pharmacol.* **1996**, *71*, 351–355.

14. Minagawa T; Sakanaka K; Inaba S; Sai Y; Tamai I; Suwa T; Tsuji A *J. Pharm. Pharmacol.* **1996**, *48*, 1016–22.

15. Yae T; Araki H; O-ogami Y; Iwasaki K; Tanabe H; Fujiwara M *Arzneimittelforschung*. **1997**, *47*, 1200–3.

16. Takamatsu, H.; Tsukada, H.; Watanabe, Y.; Cui, Y.; Kataoka, Y.; Hosoya, T.; Suzuki, M.; Watanabe, Y. *Brain Res.* **2002**, *925*, 176–182.

17. Watanabe, Y.; Matsumura, K.; Takechi, H.; Kato, K.; Morii, H.; Björkman, M.; Langstrom, B.; Noyori, R.; Suzuki, M.; Watanabe, Y. *J. Neurochem.* **1999**, *72*, 2583–2592.

18. Tanaka, M.; Kojima, C.; Muramatsu, M.; Tanabe, H. *Arzneim. Forsch.* **1995**, *45*, 967.

19. Abu Deiab, G. I.; Croatt, M. P. In *Strategies and Tactics in Organic Synthesis*; Harmata, M., Ed.; Academic Press, **2017**; Vol. 12, pp. 95–117.

20. Nagy, E. E.; Hyatt, I. F. D.; Gettys, K. E.; Yeazell, S. T.; Frempong, S. K.; Croatt, M. P. *Org. Lett.* **2013**, *15*, 586–589.

21. Bannai, K.; Tanaka, T.; Okamura, N.; Hazato, A.; Sugiura, S.; Manabe, K.; Tomimori, K.; Kurozumi, S. *Tetrahedron Lett.* **1986**, *27*, 6353–6356.

22. Hashimoto, S.; Shinoda, T.; Ikegami, S. *J. Chem. Soc. Chem. Commun.* **1988**, 1137–1139.

23. Hashimoto, S.; Shinoda, T.; Shimada, Y.; Honda, T.; Ikegami, S. *Tetrahedron Lett.* **1987**, *28*, 637–640.

24. Ishikawa, T.; Ishii, H.; Shimizu, K.; Nakao, H.; Urano, J.; Kudo, T.; Saito, S. *J. Org. Chem.* **2004**, *69*, 8133–8135.

25. Mandai, T.; Matsumoto, S.; Kohama, M.; Kawada, M.; Tsuji, J.; Saito, S.; Moriwake, T. *J. Org. Chem.* **1990**, *55*, 5671–5673.

26. Mase, T.; Sodeoka, M.; Shibasaki, M. *Tetrahedron Lett.* **1984**, *25*, 5087–5090.

27. Sheddan, N. A.; Mulzer, J. *Org. Lett.* **2005**, *7*, 5115–5118.

28. Sheddan, N. A.; Mulzer, J. *Org. Lett.* **2006**, *8*, 3101–3104.

29. Sodeoka, M.; Ogawa, Y.; Mase, T.; Shibasaki, M. *Chem. Pharm. Bull. (Tokyo)* **1989**, *37*, 586–598.

30. Tanaka, T.; Bannai, K.; Hazato, A.; Koga, M.; Kurozumi, S.; Kato, Y. *Tetrahedron* **1991**, *47*, 1861–1876.

31. Shi, L.; Yang, Z. *Eur. J. Org. Chem.* **2016**, *2016*, 2356–2368.

32. Muller, J.-L.; Rickers, A.; Leitner, W. *Adv. Synth. Catal.* **2007**, *349*, 287–291.

33. Lesage, D.; Milet, A.; Memboeuf, A.; Blu, J.; Greene, A. E.; Tabet, J.-C.; Gimbert, Y. *Angew. Chem.* **2014**, *126*, 1970–1973.

34. Strübing, D.; Beller, M. In *Catalytic Carbonylation Reactions*; Beller, M., Ed.; Topics in Organometallic Chemistry; Springer Berlin Heidelberg, **2006**; pp. 165–178.

35. López-Carrillo, V.; Echavarren, A. M. *J. Am. Chem. Soc.* **2010**, *132*, 9292–9294.

36. Grirrane, A.; Garcia, H.; Corma, A.; Álvarez, E. *ACS Catal.* **2011**, *1*, 1647–1653.

37. Wender, P. A.; Croatt, M. P.; Deschamps, N. M. *J. Am. Chem. Soc.* **2004**, *126*, 5948–5949.

38. Croatt, M. P.; Wender, P. A. *Eur. J. Org. Chem.* **2010**, *2010*, 19–32.

39. Song, B.; Knauber, T.; Gooßen, L. J. *Angew. Chem. Int. Ed.* **2013**, *52*, 2954–2958.

40. Scott, W. J.; Stille, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 3033–3040.

41. Hettrick, C. M.; Kling, J. K.; Scott, W. J. *J. Org. Chem.* **1991**, *56*, 1489–1492.

42. Felluga, F.; Forzato, C.; Ghelfi, F.; Nitti, P.; Pitacco, G.; Pagnoni, U. M.; Roncaglia, F. *Tetrahedron Asymmetry* **2007**, *18*, 527–536.

43. Luo, Y.; Herndon, J. W.; Cervantes-Lee, F. *J. Am. Chem. Soc.* **2003**, *125*, 12720–12721.

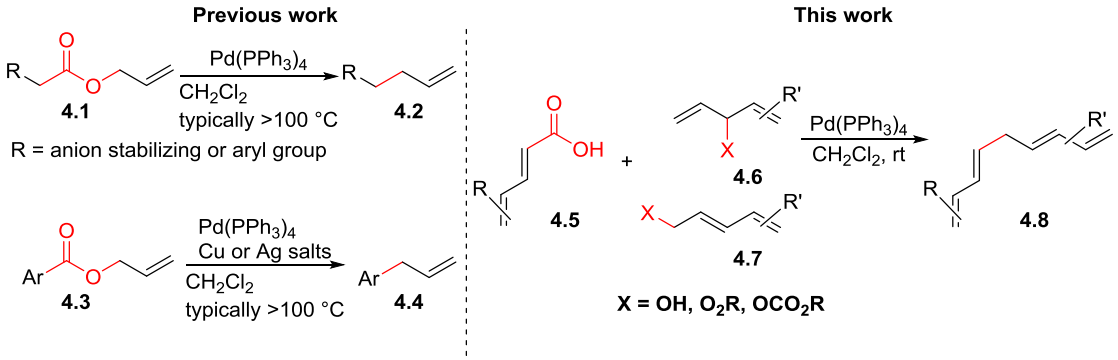
CHAPTER IV

DECARBOXYLATIVE AND DEHYDRATIVE COUPLING OF DIENOIC ACIDS AND PENTADIENYL ALCOHOLS TO FORM 1,3,6,8-TETRAENES

Abu Deiab, G. I.; Al-Huniti, M. H.; Hyatt, I. F. D.; Nagy, E. E.; Gettys, K. E.; Sayed, S. S.; Joliat, C. M.; Daniel, P. E.; Vummalaneni, R. M.; Moorehead, A. Jr.; Sargent, A. L.; Croatt, M. P. *Beilstein J. Org. Chem.* (submitted).

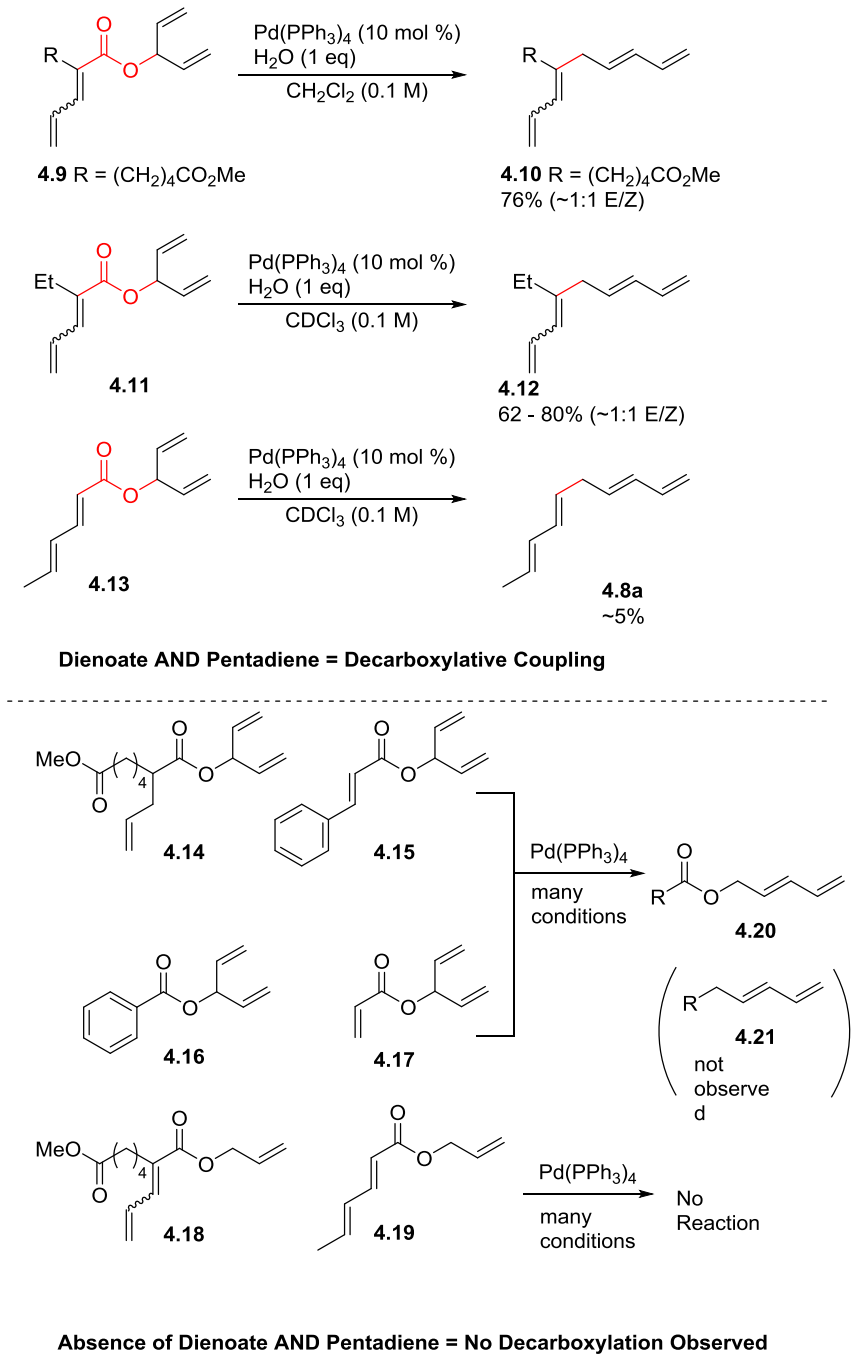
1. Background

The construction of carbon-carbon bonds where the product is electronically neutral remains a difficult and important problem in organic synthesis. Cross-coupling reactions provide avenues to these otherwise difficult molecules, but often require prefunctionalization of the coupling partners.[1-9] However, recent C-H activation research has enabled the use of further simplified starting materials.[10-18] Another approach to the formation of C-C bonds is through decarboxylative coupling reactions. This can be arrived in a one component fashion via the removal of CO_2 from an ester or in a two component manner by removal of CO_2 from a carboxylic acid and coupling this to a substrate with a benzylic or allylic leaving group.



Scheme 4.1. Prior and Current Decarboxylative Couplings.

Typical decarboxylative coupling reactions utilize an allylic or benzylic ester with either an anion-stabilizing group adjacent to the carboxyl group (i.e. carbonyl,[19-20] nitrile,[21-23] nitro,[24-25] or alkyne,[19, 26-30] Scheme 4.1), or use an aryl carboxylate[31-32] which typically requires the assistance of silver or copper (I) salts for the decarboxylative step. It is rare to use a pentadienyl leaving group,[33] or to have a diene or simple alkene adjacent to the carboxyl group.[34-37] Despite the absence of this type of reactivity, the decarboxylative coupling of a pentadienyl dienoate (**4.9**; Scheme 4.2) was so desirable for our group's synthesis of clinprost that we attempted the reaction.[38-39] Fortunately, this coupling reaction was successfully employed in our reported nine-step synthesis of clinprost.[39] A structurally related compound (**4.11**) reacted similarly, however, the sorbate derivative (**4.13**) was low yielding with the majority of the material only rearranging to the linear ester. In all three of these cases, we never observed the fully conjugated tetraene.



Scheme 4.2. Esters Examined in the Decarboxylation Reaction.

It was determined that modifying the dienoate motif yielded only the rearranged product under the reaction conditions, including the dihydro (**4.14**), cinnamate (**4.15**),

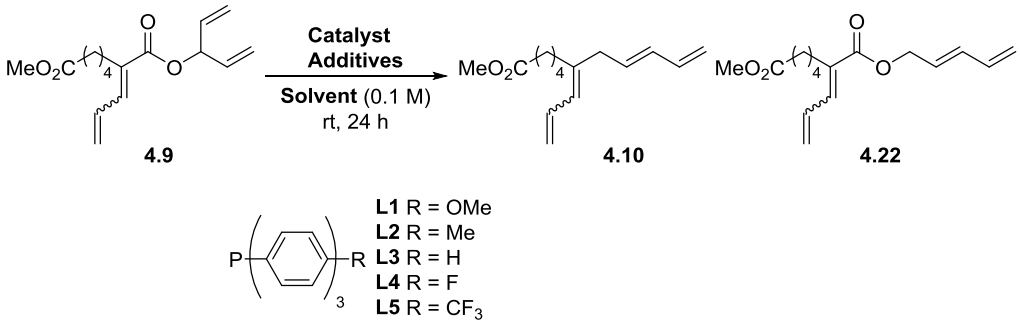
benzoate (**4.16**), and acrylate (**4.17**) analogues (Scheme 4.2). Moreover, allylic dienoates **4.18** and **4.19** gave no reaction with Pd(0) catalysis.

These results led us to the determination that there was a unique reactivity imbued to the molecule by having both the dienoate and pentadienyl moieties. Herein, are presented more details for this reaction, including the substrate scope for the intermolecular case.

2. Results and Discussion

In addition to determining the requisite nature of both the pentadienyl and dienoate groups, it was found that trace amounts of water were required (Table 4.1). For example, careful exclusion of water from reagents and solvent and performing the reaction in the glovebox led to no reaction (entry 1). Less than 1 equivalent of water allowed for a slow reaction and incomplete conversion; 1-2 equivalents was optimal with yields around 70%, and more water was not beneficial (entries 2-8). The use of equimolar amounts of methanol and water as a protic source allowed for decarboxylation to take place but with a low yield (entry 9), and the reaction run in TFE as a solvent did not result in any decarboxylation (entry 10).

Table 4.1. Optimization of the One-Component Decarboxylation Reaction.[a]



Entry	Catalyst	Solvent	Additive	Yield of 4.10 (Yield of 4.22)[b]
1	$Pd(PPh_3)_4$	CH_2Cl_2	Anhydrous	0% (99%)
2	$Pd(PPh_3)_4$	CH_2Cl_2	0.5 eq H_2O	27%
3	$Pd(PPh_3)_4$	CH_2Cl_2	1.1 eq H_2O	77%
4	$Pd(PPh_3)_4$	CH_2Cl_2	1.3 eq H_2O	72%
5	$Pd(PPh_3)_4$	CH_2Cl_2	Silylated glass, 1 eq H_2O	55% (15%)
6	$Pd(PPh_3)_4$	CH_2Cl_2	Dry glass balls	37% (24%)
7	$Pd(PPh_3)_4$	CH_2Cl_2	Wet glass balls	51%
8	$Pd(PPh_3)_4$	CH_2Cl_2/H_2O	Biphasic	49%
9	$Pd(PPh_3)_4$	CH_2Cl_2	1eq MeOH, 1 eq H_2O	33% (26%)
10	$Pd(PPh_3)_4$	TFE	Trace CH_2Cl_2	0%

11	$Pd_2(dba)_3$	CH_2Cl_2	0% PPh_3, 1 eq H_2O	0%
12	$Pd_2(dba)_3$	CH_2Cl_2	10% PPh_3, 1 eq H_2O	64%
13	$Pd_2(dba)_3$	CH_2Cl_2	20% PPh_3, 1 eq H_2O	61%
14	$Pd_2(dba)_3$	CH_2Cl_2	30% PPh_3, 1 eq H_2O	12%
15	$Pd_2(dba)_3$	CH_2Cl_2	10% **L1**, 1 eq H_2O	70%
16	$Pd_2(dba)_3$	CH_2Cl_2	10% **L2**, 1 eq H_2O	70%
17	$Pd_2(dba)_3$	CH_2Cl_2	10% **L4**, 1 eq H_2O	18%
18	$Pd_2(dba)_3$	CH_2Cl_2	10% **L5**, 1 eq H_2O	10%
19	$Pd(OAc)_2$	CH_2Cl_2	1 eq H_2O	0%
20	$Pd(OAc)_2$	CH_2Cl_2	40% PPh_3, 1 eq H_2O	10%
21	none	CH_2Cl_2	1 eq PPh_3, 1 eq H_2O	0%

[a]Reaction Conditions: Pd metal (10 mol %) and the indicated solvent and additives for 24 hours. [b]Isolated yields.

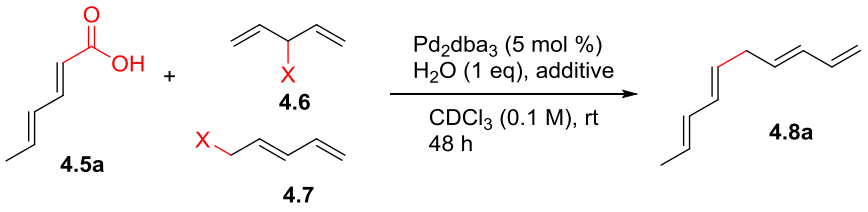
In addition to the requirement for water, it was determined that phosphine ligands were necessary (entry 11), either as ligands or as participants in the reaction as discussed later. The typical catalyst used, $Pd(PPh_3)_4$, worked well; however, it was found that a more ideal ratio of palladium metal to ligand was 1:1 or 1:2, with greater amounts of triphenylphosphine stopping the reaction when using the Pd_2dba_3 catalyst (entries 12-14). It was determined that reactions performed in the presence of electron-rich ligands had both quicker kinetics and more efficient yields (entries 15-18 and Supporting Information for kinetic information). Although not as efficient, it was found that a palladium(II) catalyst functioned in this reaction, presumably functioning as a pre-catalyst and being reduced *in situ* to the palladium(0) catalyst (entries 19 and 20). As a control reaction, it was found that no reaction occurred in the absence of palladium catalyst (entry 21).

As shown earlier, bis-allylic sorbate (**4.13**; Scheme 4.2) was found to be low yielding for the decarboxylative coupling reaction. Reactions of sorbate **4.13** monitored by ^{1}H NMR showed nearly quantitative isomerization of the bis-allylic group into a linear pentadienyl system. Increasing the reaction time did not result in greater conversion to tetraene **4.8a**, which indicates that the products may be competitively ligating and poisoning the Pd(0)-catalyst. The isomerization reaction was presumably occurring via ionization of the allylic system using Pd(0), followed by recombination of the carboxylate at the terminal position of the pentadienyl system. Based on these data, we

hypothesized that a two component reaction using a dienoic acid and bis-allylic acetate might be possible, however, the presence of both water and a carboxylic acid would increase the possibility for isomerization of the 1,3,6,8-tetraenes into the fully conjugated 1,3,5,7-tetraenes, or possibly polymerization.

Despite the low yield for decarboxylation with sorbate **4.13**, the initial attempt used inexpensive sorbic acid as the dienoic acid. Gratifyingly, this reaction was successful and it was again determined that no isomerization to the fully conjugated system was observed (Table 4.2, entry 1). Other bis-allylic leaving groups were studied and, unexpectedly, it was determined that divinylcarbinol was superior (entries 1-6). In fact, the better leaving groups were either slow or ineffective. This could be due to the less basic leaving groups not sufficiently deprotonating sorbic acid, which may be required for this reaction as is discussed mechanistically later (Scheme 4.3). Similar to the single component reaction, more than two equivalents of phosphine, relative to palladium metal, was detrimental (compare entries 12-14 of Table 4.1 with entries 6-8 of Table 4.2), however, the reaction was successful using $Pd(PPh_3)_4$ (entry 9).

Table 4.2. Optimization of the Two-Component Decarboxylation Reaction.[a]



Entry	Pentadienyl Group	Additive	Yield[b]

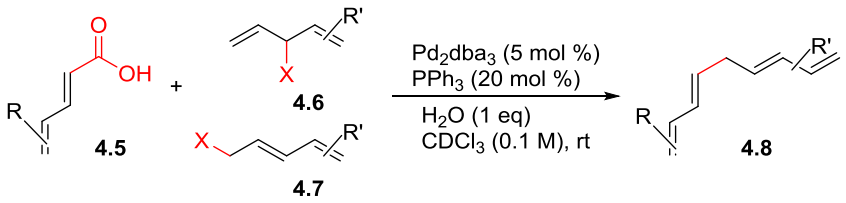
1	**4.6a**, X = OAc	PPh_3 (20 mol %)	12%
2	**4.6b**, X = OCO_2Me	PPh_3 (20 mol %)	35%
3	**4.6c**, X = OBz	PPh_3 (20 mol %)	11%
4	**4.6d**, X = $O_2C(4\text{-}CF_3Ph)$	PPh_3 (20 mol %)	6%
5	**4.7a**, X = Br	PPh_3 (20 mol %)	0%
6	**4.6e**, X = OH	PPh_3 (20 mol %)	40%
7	**4.6e**, X = OH	PPh_3 (10 mol %)	18%
8	**4.6e**, X = OH	PPh_3 (30 mol %)	24%
9[c]	**4.6e**, X = OH	NA	28%

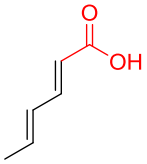
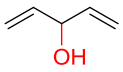
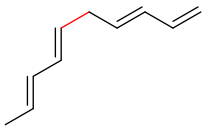
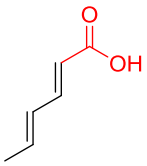
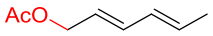
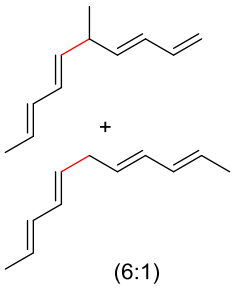
[a]Reaction Conditions: Sorbic acid (**4.5a**, 1 eq), pentadienyl group (**4.6** or **4.7**, 1 eq), $Pd_2(dba)_3$•$CHCl_3$ (5 mol %) unless indicated otherwise, H_2O (1 eq), in $CDCl_3$ for 48 hours. [b]NMR yields. [c]$Pd(PPh_3)_4$ (10 mol %).

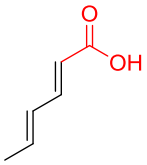
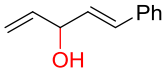
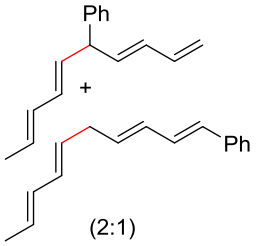
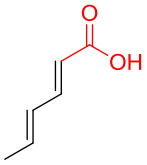
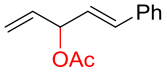
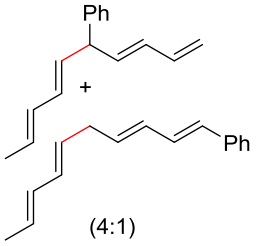
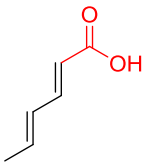
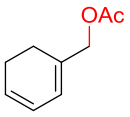
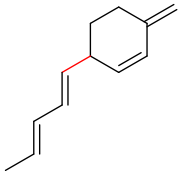
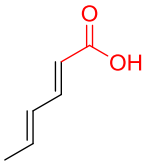
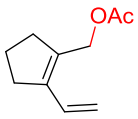
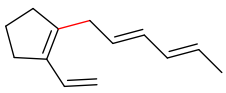
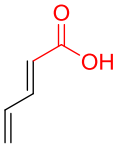
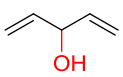
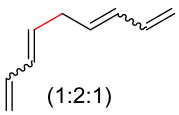
To further understand this interesting decarboxylative coupling reaction, a handful of different pentadienyl groups and dienoic acids were examined (Table 4.3). It was found that both a methyl or phenyl substituent on the alcohol derivative would result in branched product **4.8b** or **4.8d** being the major product with approximately 10% of the product mixture being the linear product (entries 2-4). The yields for these reactions were low, but the remaining material was typically starting material and the ester where the acid and alcohol are coupled together. With these highly unsubstituted tetraene products, it is hypothesized that the product may be sequestering the palladium catalyst. Two cyclic

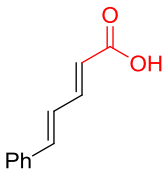
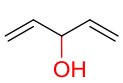
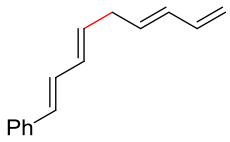
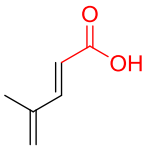
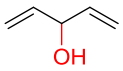
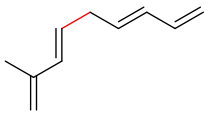
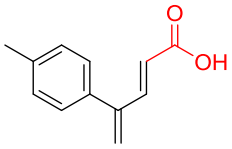
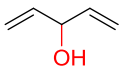
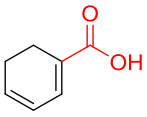
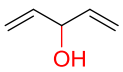
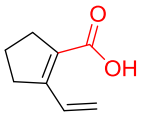
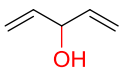
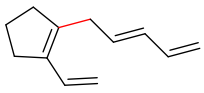
dienyl acetates were also studied (entries 5 and 6) and they yielded tetraenes **4.8f** and **4.8g**. The dienes of entries 5 and 6 could have formed additional isomers by coupling to the other end of the pentadienyl group, but only one regioisomer was observed.

Table 4.3. Substrate Scope for the Two-Component Decarboxylation Reaction.[a]



Entry	Dienoic Acid	Pentadienyl Group	Yield (Product)[b]
1	 **4.5a**	 **4.6e**	 40% (**4.8a**)
2	 **4.5a**	 **4.7b**	 (6:1) 2% (**4.8b/4.8c**)

3	 **4.5a**	 **4.6f**	 (2:1)	21%, 17%[c] (**4.8d/4.8e**)
4	 **4.5a**	 **4.6g**	 (4:1)	13%, 6%[c] (**4.8d/4.8e**)
5	 **4.5a**	 **4.7c**		16%[c] (**4.8f**)
6	 **4.5a**	 **4.7d**		18%[c] (**4.8g**)
7	 **4.5a**	 **4.6e**	 (1:2:1)	14% (**4.8h/4.8i/4.8j**)

	4.5b		
8	 **4.5c**	 **4.6e**	 27% (**4.8k**)
9	 **4.5d**	 **4.6e**	 36% (**4.8l**)
10	 **4.5e**	 **4.6e**	Decomposition
11	 **4.5f**	 **4.6e**	Decomposition
12	 **4.5g**	 **4.6e**	 76% (**4.8m**)

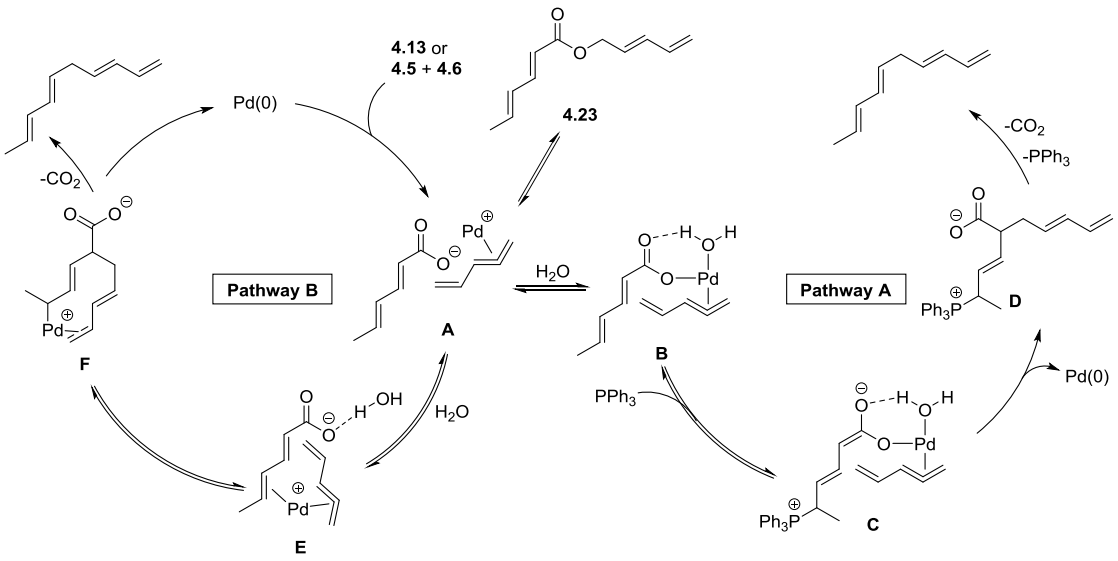
[a]Reaction Conditions: Dienoic acid (**4.5**, 1 eq), pentadienyl group (**4.6** or **4.7**, 1 eq), H_2O

(1 eq), $Pd_2(dba)_3$•$CHCl_3$ (5 mol %), PPh_3 (20 mol %), in $CDCl_3$ for 48 hrs. [b]NMR yields. [c]Isolated yields.

With respect to the dienoic acid, it was determined that the unsubstituted compound, pentadienoic acid, underwent decarboxylative coupling, although as a mixture of *E*/*E*, *E*/*Z*, and *Z*/*Z* isomers (entry 7). Alkyl- and aryl-substituents were possible on the dienoate with the exception of an aryl group at the gamma position (entries 8-10). Two cyclic dienoic acids were synthesized[40-41] and while the cyclohexadienoic acid did not decarboxylate (entry 11), the vinylcyclopentenoic acid had a good yield of a complex tetraene (entry 12).

Based on the information obtained during optimization and screening of compounds, two potential mechanisms are proposed (Scheme 4.3). Both options allow for the one (**4.13**) or two (**4.5** and **4.6**) component process to be used while also allowing for the reversible formation of linear ester **4.23**. Pathway A involves a Morita-Baylis-Hilmann type process. The role of water would be to hydrogen bond to the carboxylate to make the system more electrophilic (**B**). This would accelerate the addition of the phosphine to generate zwitterion **C**.[42] Preliminary modeling for this ion indicates that both the electrophilic terminal vinyl group of the pentadienyl ligand and the nucleophilic α-carbon are in close proximity to one another. Formation of the carbon-carbon bond would then regenerate the Pd(0) catalyst and phosphonium carboxylate **D**. Decarboxylative elimination of the phosphine results in formation the 1,3,6,8-tetraene. It

is proposed for Pathway A that the dienoate is required so that the α-carbon is not blocked by the bulky phosphine group since it can add in a 1,6- or 1,4-manner, both reversibly.



Scheme 4.3. Possible Mechanistic Pathways.

Alternatively, Pathway B has the palladium catalyst coordinate to one of the alkenes of the dienoate instead of the carboxylate (**E**). It is proposed that a water cluster around the carboxylate would enable this process by hydrogen bonding to the carboxylate. The conversion of **E** to **F** would form the C-C bond by having the palladium catalyst convert from one type of η^3-allyl and π-complex (**E**) to a different allyl/π-complex (**F**). Finally, decarboxylative reduction of the palladium would release the product while regenerating the catalyst. Preliminary computational calculations using NEB[43] support Pathway B and the HOMO of the transition state between **E** and **F** (Figure 4.1) calculated using the Gaussian 09 implementation of DFT with a B3LYP functional,

6-31g* basis, and polarized continuum model of solvation for DCM, shows close proximity of two in-phase orbitals for the requisite C-C bond, whereas removal of any one of the alkenes from this structure would lead to anti-bonding relationships to bond to the alpha carbon.

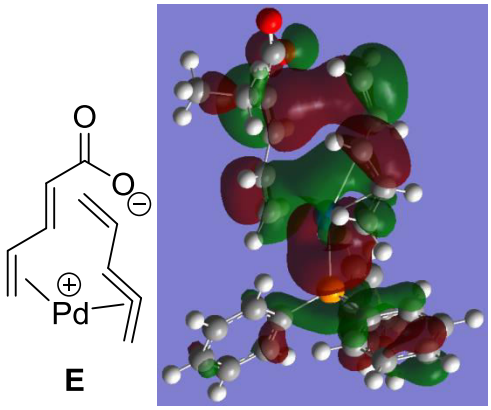


Figure 4.1. Calculated HOMO of Transition State between **E** and **F**.

3. Conclusion

In summary, we present information that is of value to advancing the area of metal-catalyzed decarboxylative coupling reactions, specifically those of pentadienyl dienoates that do not require an anion-stabilizing group, are run at ambient temperature, and can utilize the more accessible alcohol for a leaving group. This reaction was advanced to be possible in a two component fashion, allowing for the conversion of dienoic acids and pentadienyl alcohols into 1,3,6,8-tetraenes with the only stoichiometric byproducts being water and carbon dioxide. These reactions currently require a diene motif with each coupling partner, but the product maintains the independent reactivity opportunities of these isolated dienes as opposed to forming the fully conjugated, 1,3,5,7-

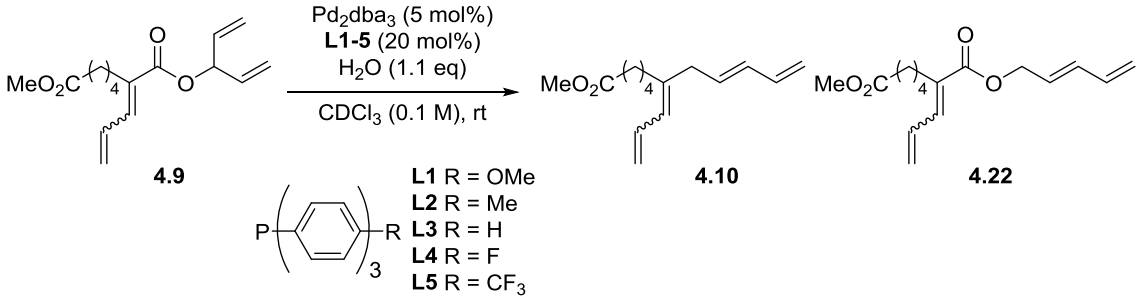
tetraene. A variety of substrates were explored where each of the unique positions on the coupling partners was modified and two different mechanistic pathways are presented. A more in-depth mechanistic analysis to improve the yields and to explore other reactivity possibilities based on this process are currently being studied and will be published in due time.

4. Experimental and Charecterization Data

4.1 General Information

All anhydrous reactions were performed in oven dried glassware under a nitrogen atmosphere. Unless otherwise noted, all solvents and reagents were obtained from commercial sources and used without further purification. NMR yields were obtained by using dimethyl terphthalate as an internal standard in a $CDCl_3$ solution. Chromatographic purification was performed using silica gel (60 Å, 32-63 μm). NMR spectra were recorded in $CDCl_3$ using a JEOL ECA 400 spectrometer (400 MHz for ^{1}H, 100 MHz for ^{13}C, and 376.5 MHz for ^{19}F) and JEOL ECA spectrometer (500 MHz for ^{1}H, 125 MHz for ^{13}C, and 470 MHz for ^{19}F). Coupling constants, *J*, are reported in hertz (Hz) and multiplicities are listed as singlet (s), doublet (d), triplet (t), quartet (q), quintet (quint), doublet of doublets (dd), triplet of triplets (tt), multiplet (m), etc. High Resolution Mass Spectra were acquired on a Thermo Fisher Scientific LTQ Orbitrap XL MS system. Low Resolution Mass Spectrometry was accomplished using Gas Chromatography on a Shimadzu GC2010-QP2010S instrument.

4.2 Kinetic Data for Different Phosphine Ligands



To a prepared solution of Pd_2dba_3•$CHCl_3$ (5 mol %) and designated ligand (see above and Chart; 20 mol %) in $CDCl_3$ (0.1 M) was added pentadienyl dienoate **4.9** (20 mg, 0.072 mmol) at ambient temperature. ^{1}H NMR spectra were obtained upon dissolution of the reagents and subsequent ^{1}H NMR spectra were obtained every 90 minutes. The formation of the product **4.10** was monitored and plotted versus time in (Figure 4.2).

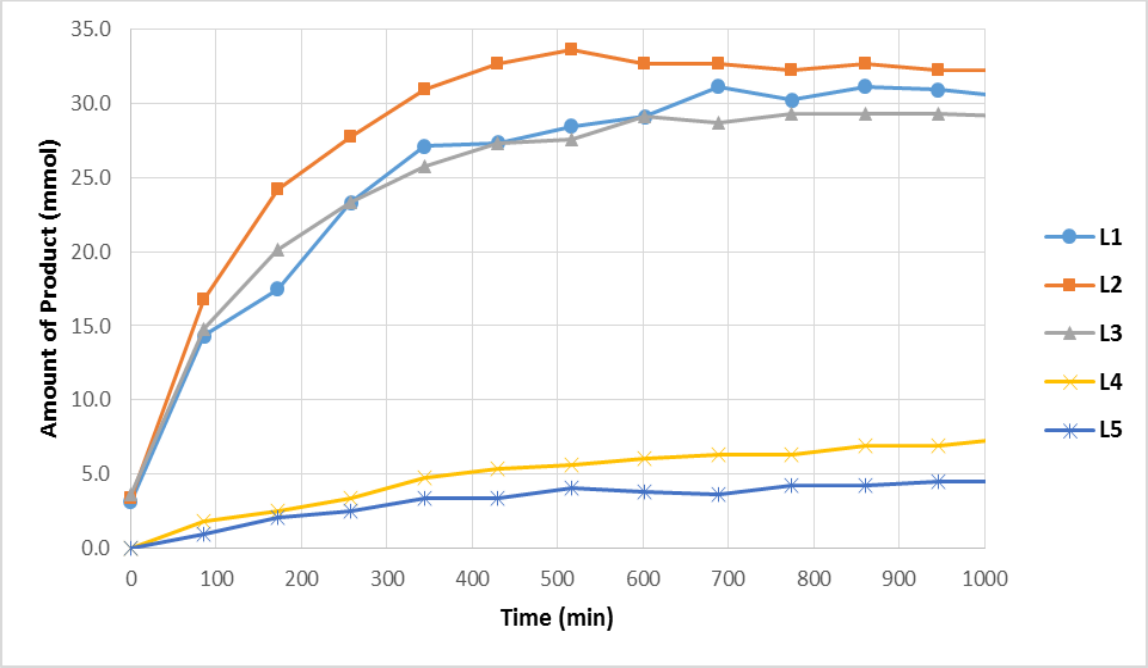
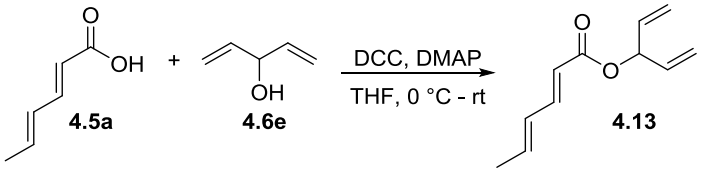


Figure 4.2. Formation of Product **4.10** Using Different Phosphine Ligands.

4.3 Experimental Procedures and Characterization of Pentadienyl Dienoates



Penta-1,4-dien-3-yl (2*E*,4*E*)-hexa-2,4-dienoate, 4.13

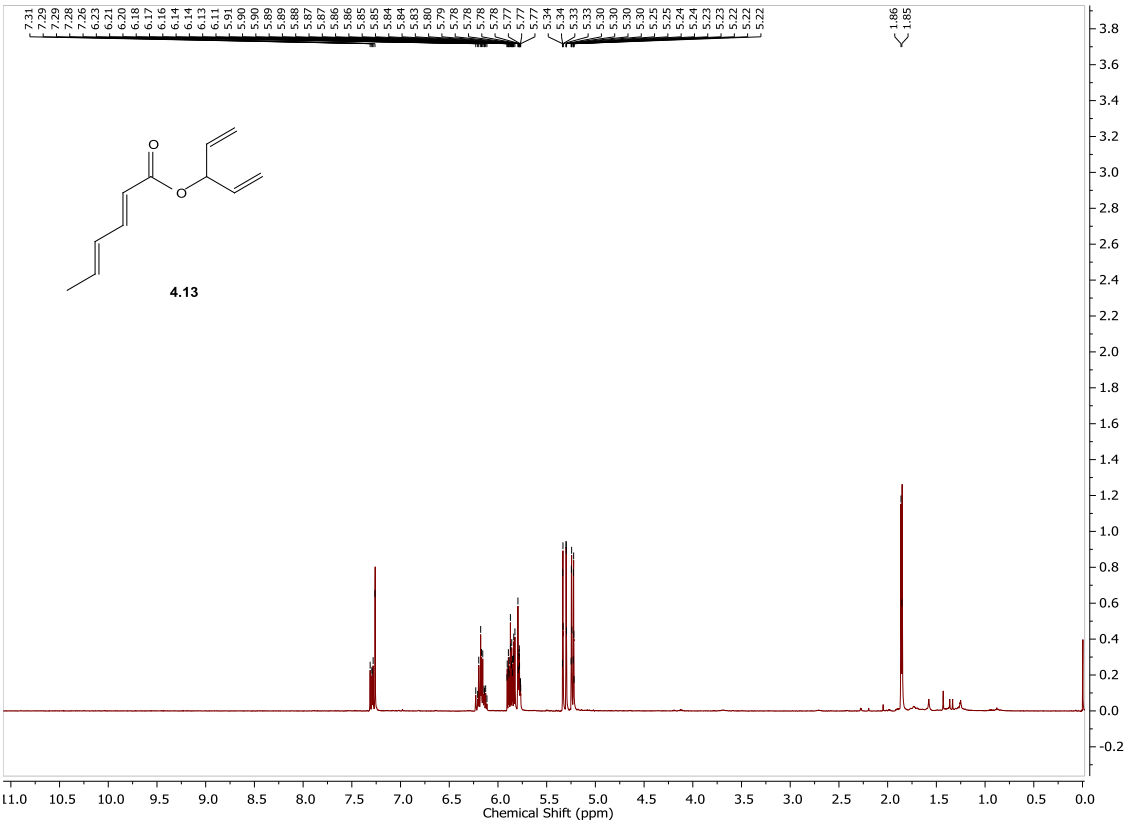
To an ice-cooled solution of DCC (0.83 g, 4.0 mmol) in THF (15 mL) were sequentially added sorbic acid (0.50 g, 2.8 mmol), 1,4-pentadien-3-ol **4.6e** (0.34 mL, 3.4 mmol) and DMAP (70 mg, 0.57 mmol). The reaction was allowed to warm to room temperature for 18 hours before it was filtered through Celite® and washed with hexane. The filtrate was concentrated and purified via silica gel chromatography (95:5,

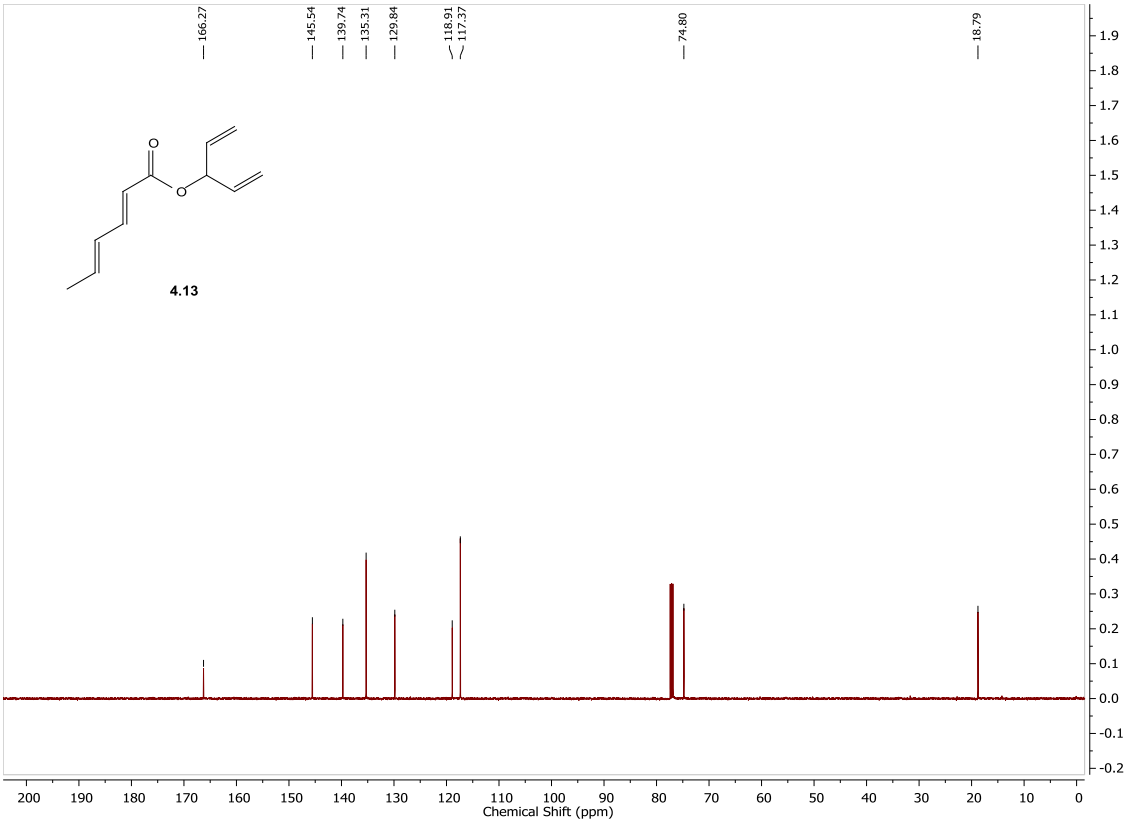
hexanes/EtOAc) to yield ester **4.13** (0.42 g, 82%) as a colorless oil. R_f = 0.78 (88:12, hexanes/EtOAc).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.26 (m, 1H), 6.23 – 6.11 (m, 1H), 5.91 – 5.83 (m, 3H), 5.80 – 5.77 (m, 2H), 5.30 (dt, J_d = 17.0 Hz, J_t = 1.5 Hz, 2H), 5.22 (dt, J_d = 10.0 Hz, J_t = 1.0 Hz, 2H), 1.86 (d, J = 6.0 Hz, 3H) ppm.

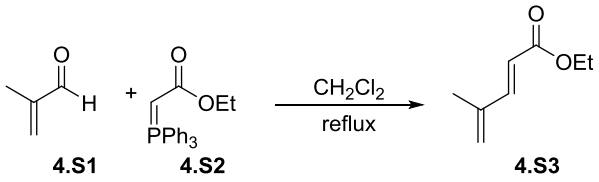
^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 145.5, 139.7, 135.3 (2C), 129.8, 118.9, 117.4 (2C), 74.8, 18.8 ppm.

HRMS (APCI): calcd. for $[C_{11}H_{14}O_2+H]^+$: 179.1067, found: 179.1066.





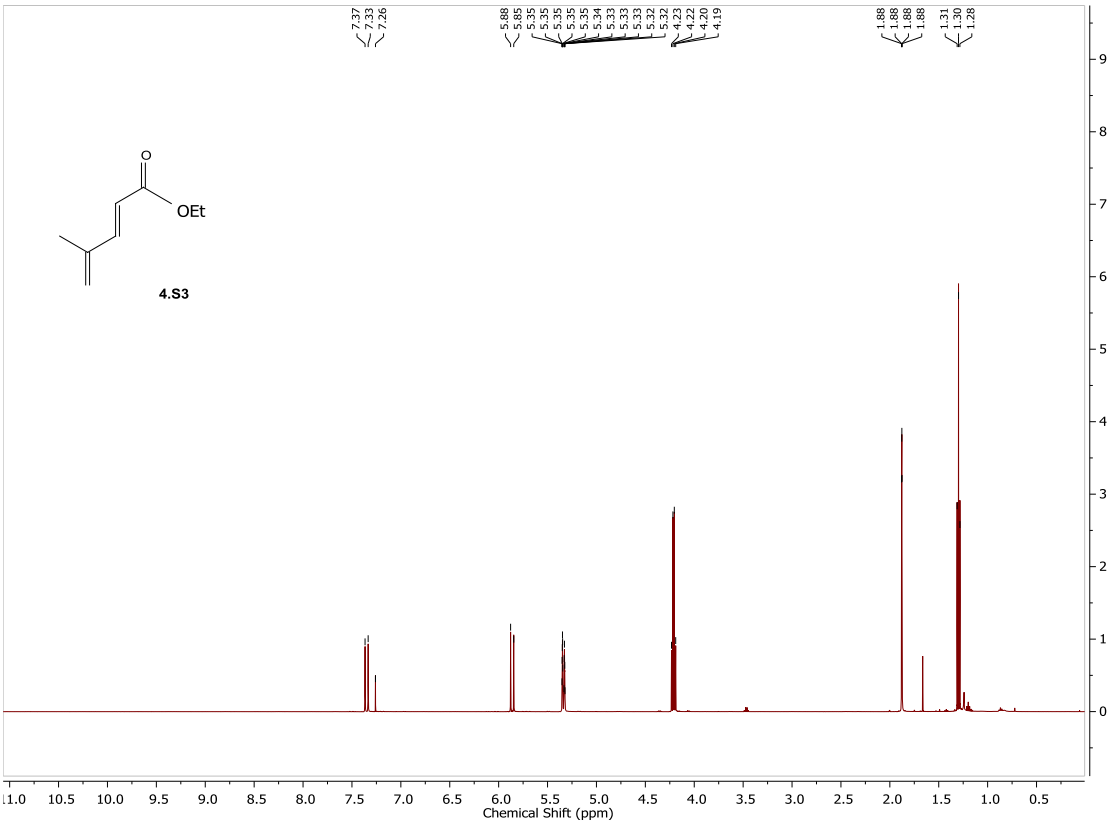
4.4 Experimental Procedures and Characterization of Dienoic Acids

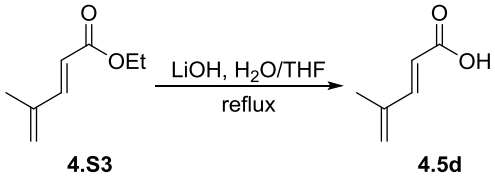


(*E*)-ethyl 4-methylpenta-2,4-dienoate, 4.S3

Following a previously reported procedure, ester **4.S3** was synthesized as a light yellow oil, (1.2 g, 70%). R_f = 0.40 (95:5, hexanes/EtOAc). ^{1}H and ^{13}C NMR are consistent with literature reports.[44]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (d, *J* = 16.0 Hz, 1H), 5.86 (d, *J* = 16.0 Hz, 1H), 5.36 – 5.32 (m, 2H), 4.21 (q, *J* = 7.2 Hz, 2H), 1.88 (dd, *J* = 1.4, 0.8 Hz, 3H), 1.30 (t, *J* = 7.1 Hz, 3H) ppm.

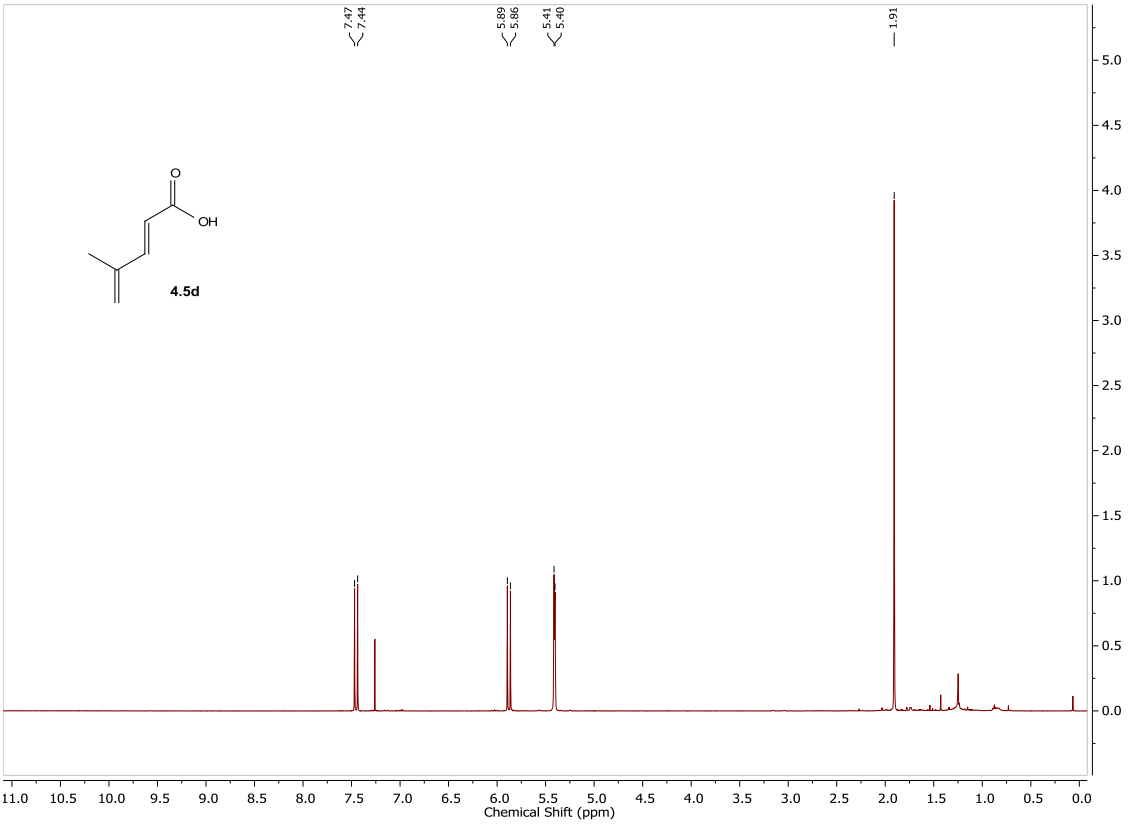


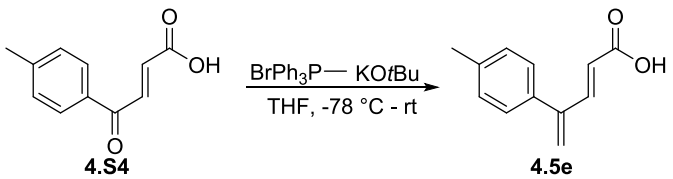


(*E*)-ethyl 4-methylpenta-2,4-dienoic acid, 4.5d

Following a previously reported procedure, acid **4.5d** was synthesized as an off-white solid, (71 mg, 90%), R_f = 0.55 (50:50, hexanes/EtOAc, large streak). ^{1}H and ^{13}C NMR are consistent with literature reports.[44]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (d, *J* = 15.7 Hz, 1H), 5.88 (d, *J* = 15.7 Hz, 1H), 5.41 (s, 1H), 5.40 (s, 1H), 1.91 (d, *J* = 1.0 Hz, 3H) ppm.



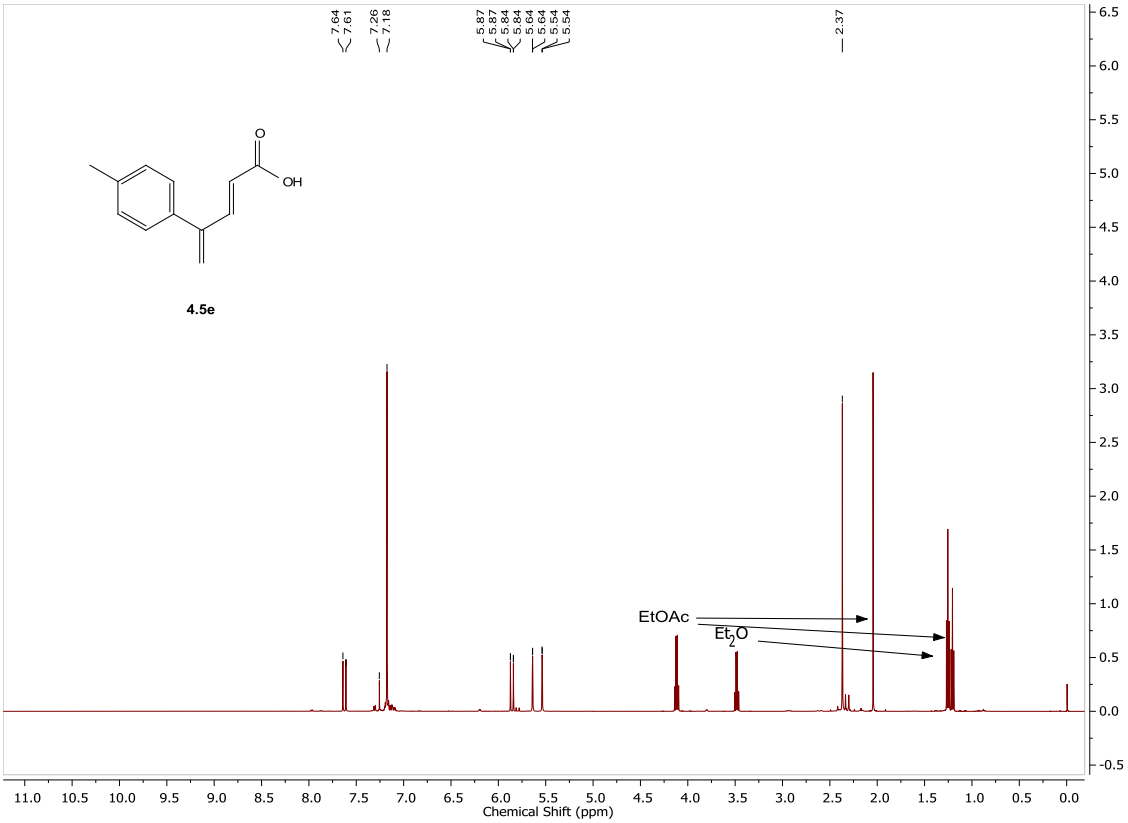


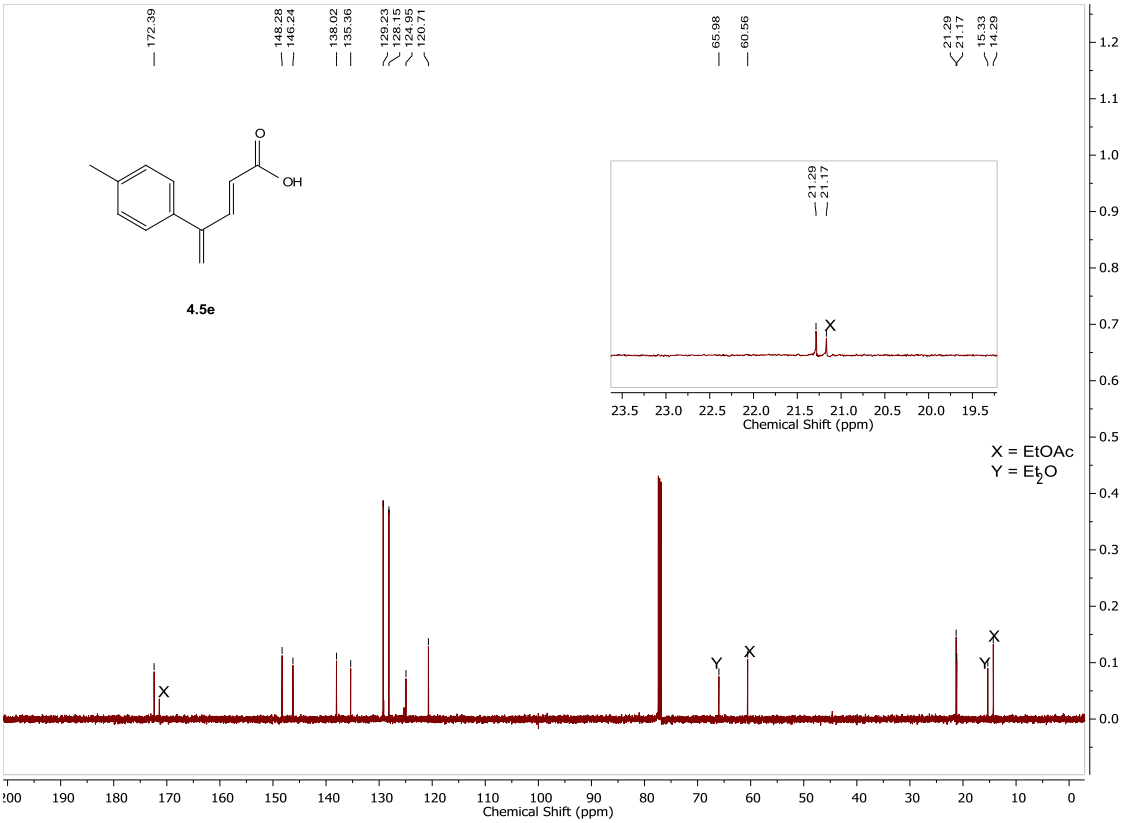
(*E*)-4-(*p*-tolyl)penta-2,4-dienoic acid, 4.5e

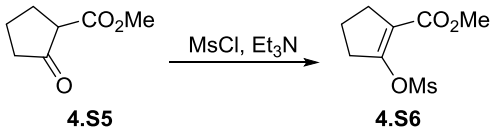
To a solution of *trans*-3-(4-methylbenzoyl)acrylic acid **4.S4** (1.0 g, 5.2 mmol) and methyltriphenylphosphonium bromide (2.8 g, 7.9 mmol) at -78 °C in THF (70 mL) was added dropwise a solution of potassium *t*-butoxide (1.1 g, 10 mmol) in THF (12 mL). The reaction mixture was allowed to warm gradually to room temperature for 2.5 hours and turned from yellow to dark orange. The mixture was quenched with water at 0 °C, acidified with 10% aqueous HCl to a pH ~ 3 and extracted 3x with EtOAc. The combined organic layers were dried using Na_2SO_4 and concentrated. Purification via silica gel chromatography (95:5, hexanes/EtOAc) yielded acid **4.5e** (450 mg, 50%) as a yellow oil. R_f = 0.79 (95:5, hexanes/EtOAc). This compound was found to be unstable at room temperature for several hours and it was taken directly to the next reaction. Due to the instability, HRMS data was not obtained and the NMR spectra contained moderate solvent impurities.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 15.9 Hz, 1H), 7.18 (s, 4H), 5.86 (d, *J* = 15.8 Hz, 1H), 5.64 (s, 1H), 5.54 (s, 1H), 2.35 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 148.3, 146.2, 138.0, 135.4, 129.2 (2C), 128.2 (2C), 124.9, 120.7, 21.3 ppm.

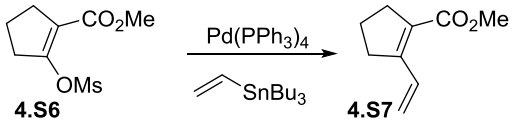

7.64
7.61
7.26
7.18
5.87
5.87
5.84
5.84
5.64
5.64
5.54
5.54
2.37
O
OH
4.5e
EtOAc
Et2O
Chemical Shift (ppm)





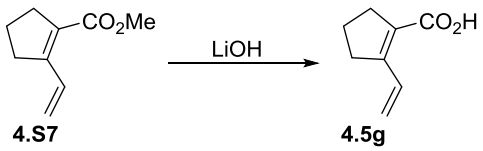
Methyl 2-((methylsulfonyl)oxy)cyclopent-1-enecarboxylate, 4.S6

See Chapter III-section 4.3, p.112 compound **3.26** for experimental details.



Methyl 2-vinylcyclopent-1-ene-1-carboxylate, 4.S7

See Chapter III-section 4.3, page 113 compound **3.27** for experimental details.



2-Ethenyl-1-cyclopentenecarboxylic Acid, 4.5g

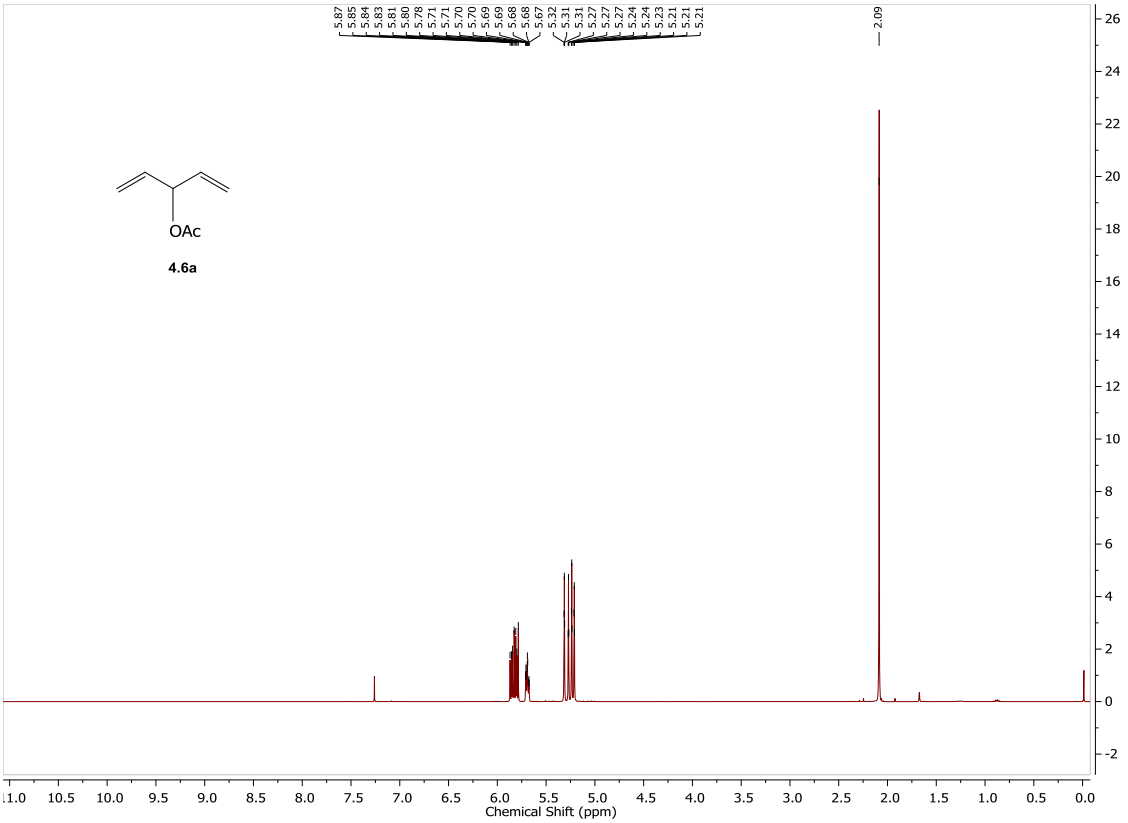
See Chapter III-section 4.3, page 114 compound **3.28** for experimental details.

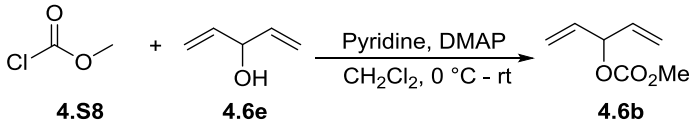
4.5 Experimental Procedures and Characterization of Pentadienyl Groups

Penta-1,4-dien-3-yl acetate, 4.6a

Following a previously reported procedure, acetate **4.6a** was synthesized as a colorless liquid, (1.6 g, 64%). R_f = 0.44 (80:20, hexanes/EtOAc). ^{1}H and ^{13}C NMR are consistent with literature reports.[45]

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.83 (ddd, J = 17.0, 10.5, 6.0 Hz, 2H), 5.69 (tt, J = 6.0, 1.2 Hz, 1H), 5.29 (dt, J_d = 17.1 Hz, J_t = 1.1 Hz, 2H), 5.22 (dt, J_d = 10.5 Hz, J_t = 1.2 Hz, 2H), 2.09 (s, 3H) ppm.



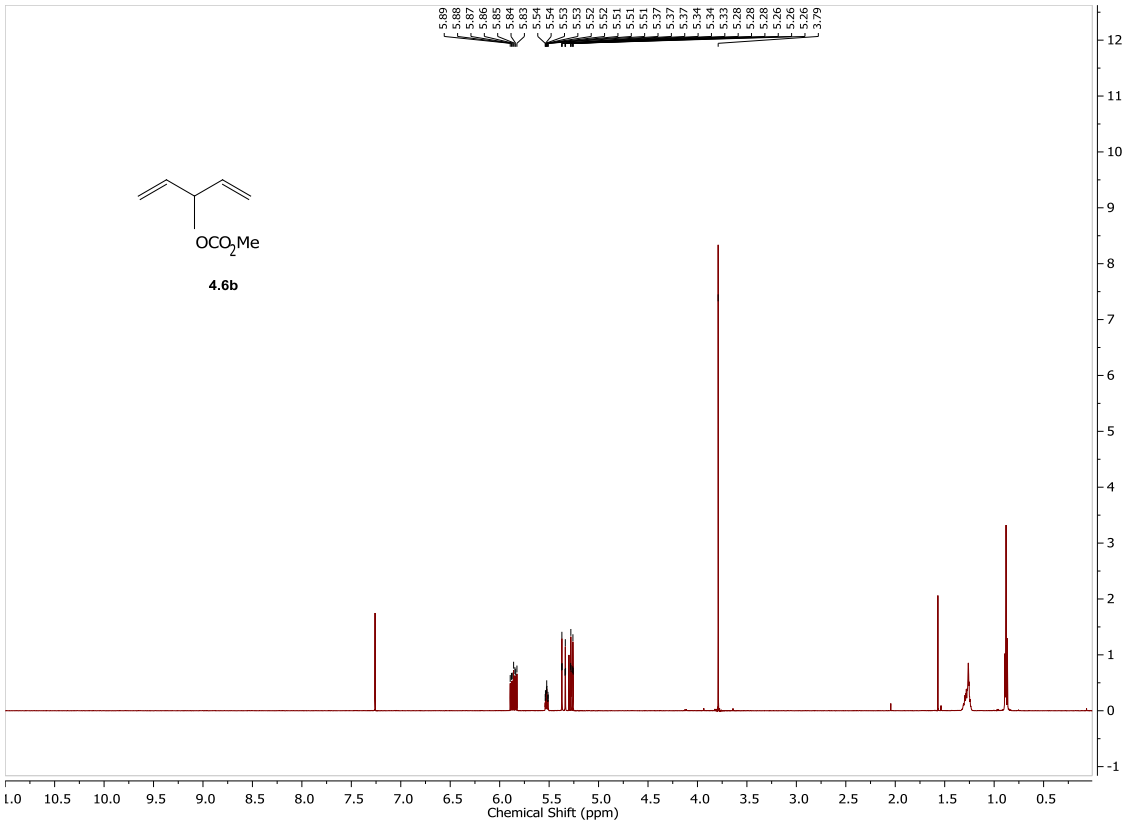


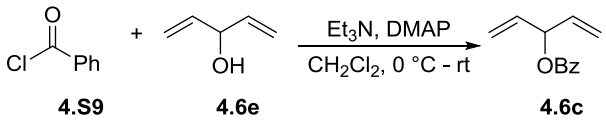
4.S8 **4.6e** **4.6b**

Methyl penta-1,4-dien-3-yl carbonate, 4.6b

Following a previously reported procedure, carbonate **4.6b** was synthesized as a yellow liquid, (202 mg, 36%). R_f = 0.30 (80:20, hexanes/EtOAc). ^{1}H and ^{13}C NMR are consistent with literature reports.[46]

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.90 – 5.82 (m, 2H), 5.52 (tt, J = 6.3, 1.2 Hz, 1H), 5.35 (dt, J_d = 17.2, J_t = 1.2 Hz, 2H), 5.27 (dt, J_d = 10.5, J_t = 1.2 Hz, 2H), 3.79 (s, 3H) ppm.


5.89
5.88
5.87
5.86
5.85
5.84
5.83
5.54
5.54
5.53
5.53
5.52
5.52
5.51
5.51
5.51
5.37
5.37
5.37
5.34
5.34
5.33
5.28
5.28
5.28
5.26
5.26
5.26
3.79
OCO2Me
4.6b
Chemical Shift (ppm)



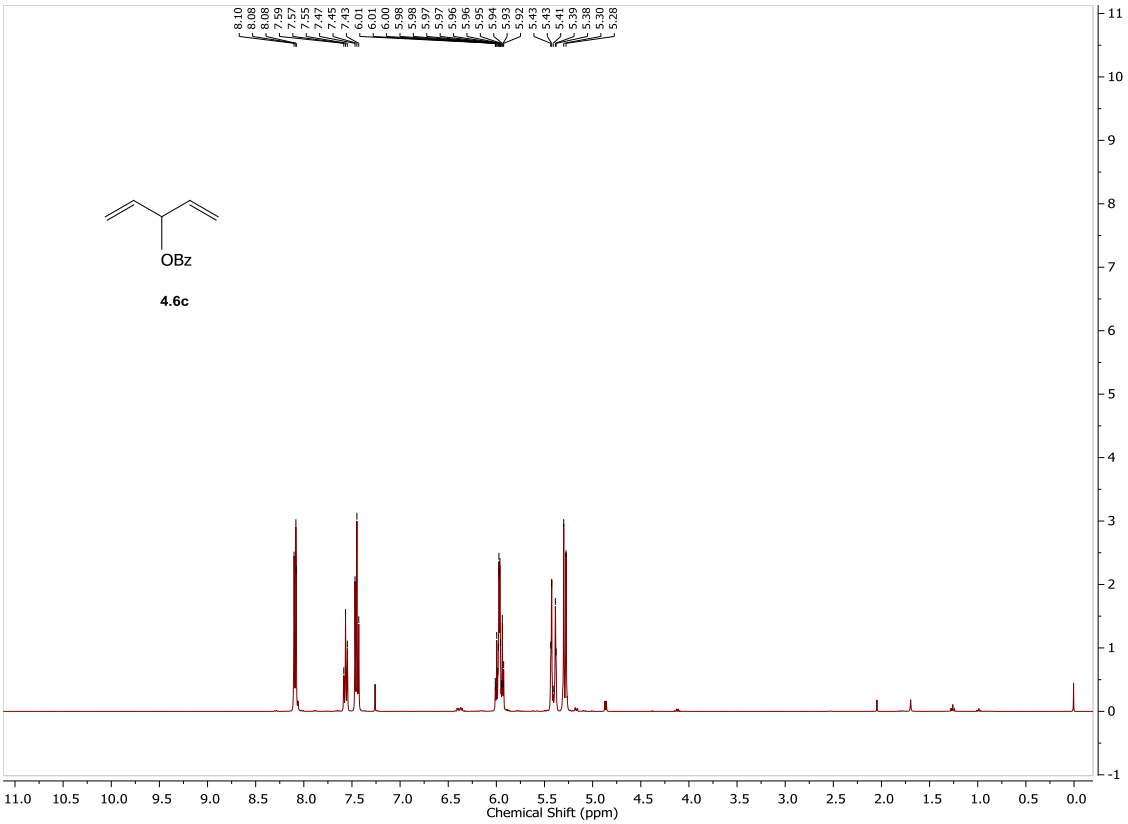
Penta-1,4-dien-3-yl benzoate, 4.6c

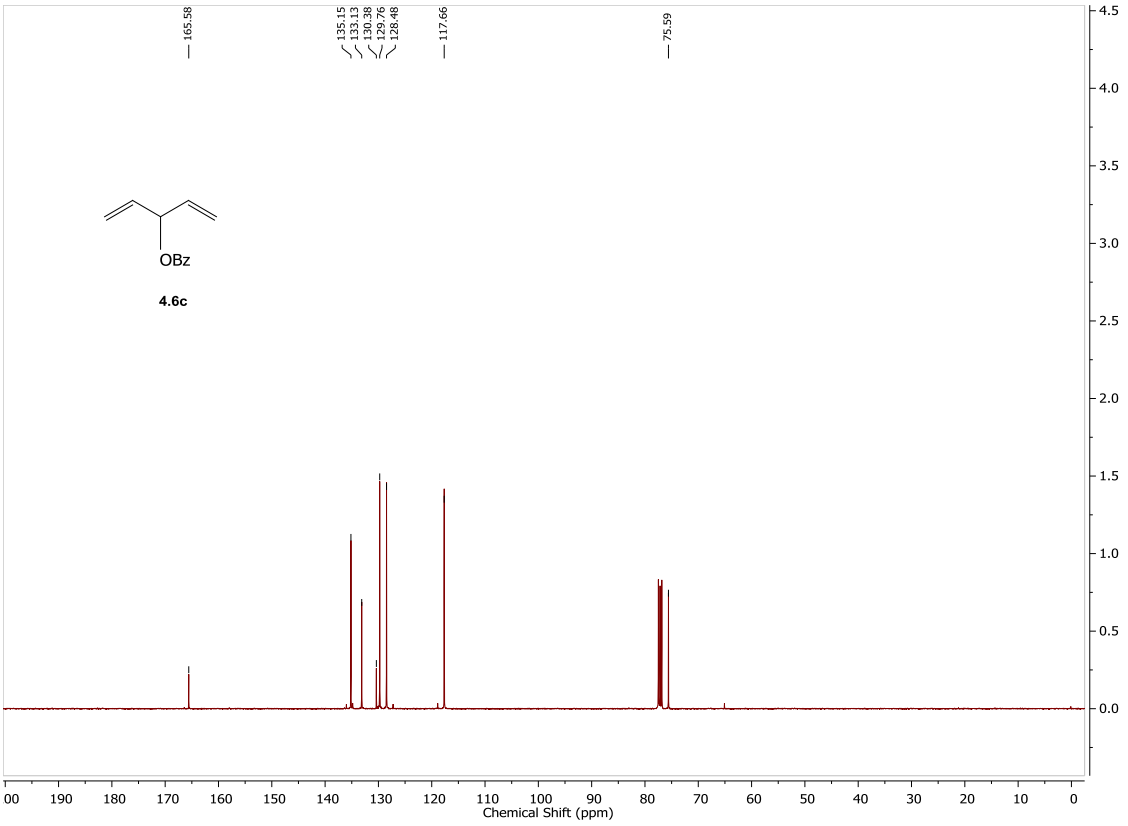
Benzoyl chloride **4.S9** (5.2 mL, 45 mmol), Et_3N (6.3 mL, 45 mmol) and DMAP (183 mg, 1.5 mmol) were sequentially added slowly to a precooled solution of 1,4-pentadien-3-ol **4.6e** (1.5 mL, 15 mmol) in CH_2Cl_2 (33 mL) at 0 °C. After stirring for 18 hours at room temperature, the reaction was quenched with saturated NH_4Cl solution, washed with hexane and extracted with CH_2Cl_2. The organic layers were combined, dried using Na_2SO_4 and concentrated. Purification via silica gel chromatography (90:10, hexanes/EtOAc) yielded benzoate **4.6c** (1.4 g, 48%) as a colorless liquid. $R_f = 0.18$ (90:10, hexanes/EtOAc).

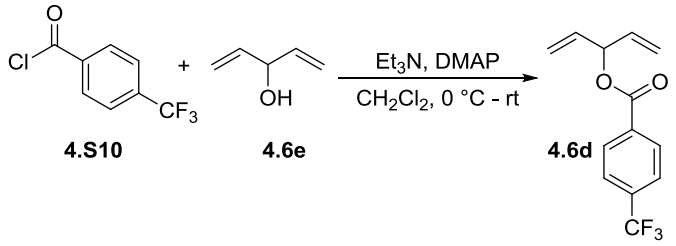
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 – 8.08 (m, 2H), 7.57 (t, J = 7.4 Hz, 1H), 7.45 (t, J = 7.7 Hz, 2H), 6.01 – 5.92 (m, 3H), 5.43 – 5.38 (m, 2H), 5.29 (d, J = 9.6 Hz, 2H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 135.1 (2C), 133.1, 130.4, 129.8 (2C), 128.5 (2C), 117.7 (2C), 75.6 ppm.

HRMS (APPI) calcd. for $[C_{12}H_{12}O_2+H]^+$: 189.0910, found: 189.0909.


8.10
8.08
8.08
7.59
7.57
7.55
7.47
7.45
7.43
6.01
6.00
5.98
5.98
5.97
5.97
5.96
5.96
5.95
5.94
5.93
5.92
5.43
5.43
5.41
5.39
5.38
5.30
5.28
OBz
4.6c
Chemical Shift (ppm)





Penta-1,4-dien-3-yl 4-(trifluoromethyl)benzoate, 4.6d

To a solution of 1,4-pentadien-3-ol **4.6e** (0.25 mL, 2.6 mmol) in CH_2Cl_2 (26 mL) precooled to 0 °C, were sequentially added 4-(trifluoromethyl)benzoyl chloride **4.S10** (0.4 mL, 2.6 mmol), Et_3N (1.1 mL, 7.7 mmol) and DMAP (31 mg, 0.25 mmol). After stirring for 18 hours at room temperature, the reaction was quenched with saturated NH_4Cl solution, washed with hexane and extracted with CH_2Cl_2. The organic layers were

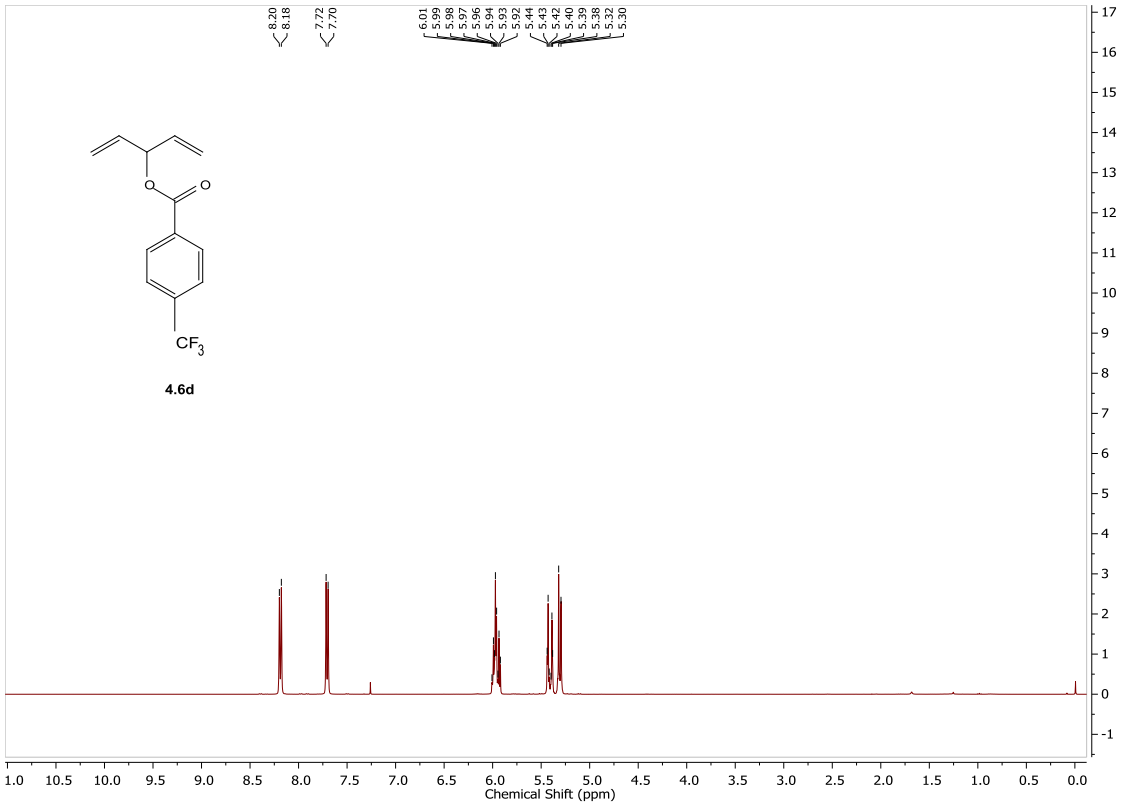
combined and dried using Na_2SO_4 and concentrated. Purification via silica gel chromatography (90:10, hexanes/EtOAc) yielded benzoate **4.6d** (529 mg, 83%) as a faint yellow liquid. R_f = 0.82 (80:20, hexanes/EtOAc).

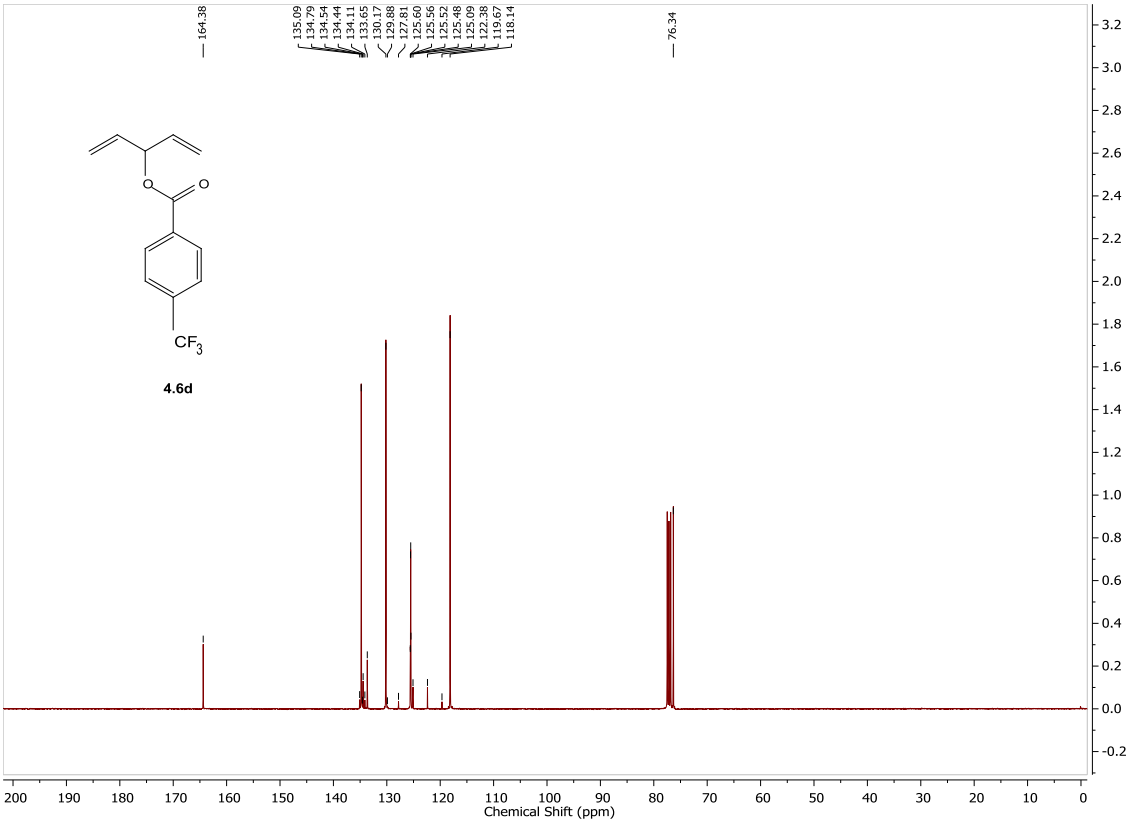
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, *J* = 8.2 Hz, 2H), 7.71 (d, *J* = 8.2 Hz, 2H), 6.01 – 5.92 (m, 3H), 5.44 – 5.38 (m, 2H), 5.31 (d, *J* = 9.6 Hz, 2H) ppm.

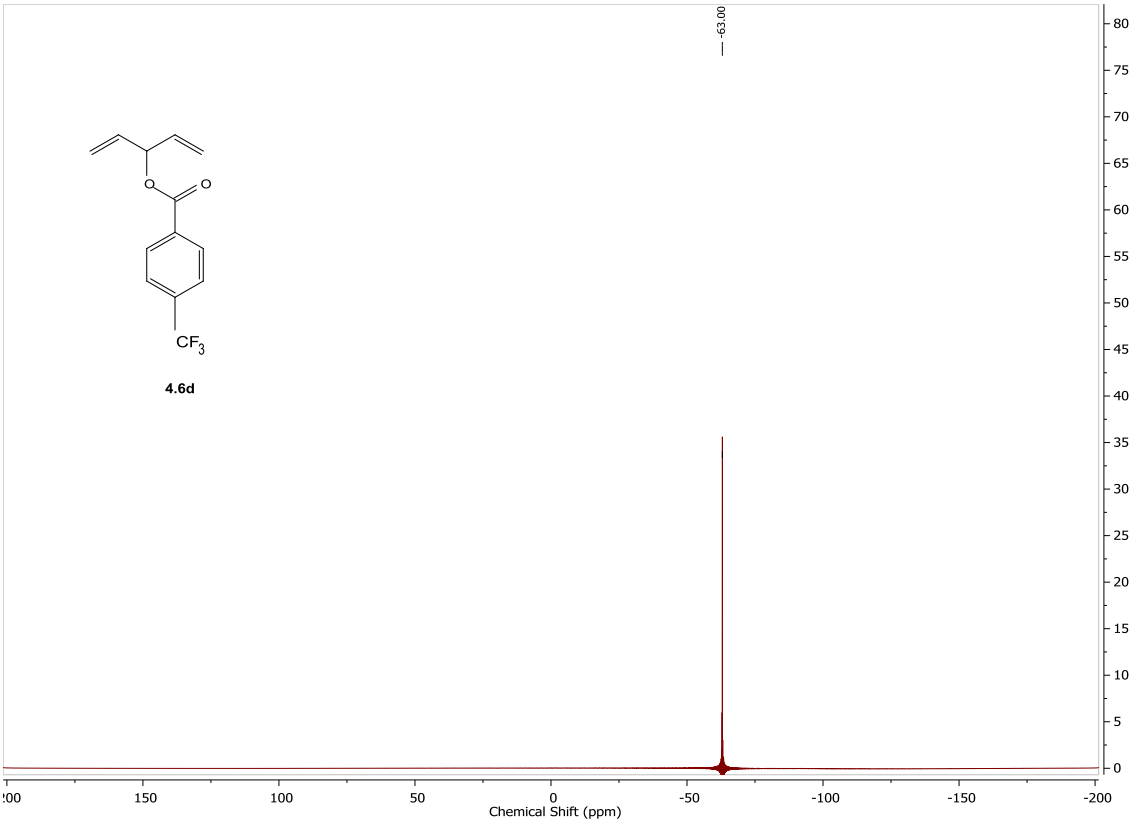
^{13}C NMR (100 MHz, $CDCl_3$) δ 164.4, 134.8 (2C), 134.5 (q, J_{C-F} = 45 Hz, 1C), 133.7, 130.2 (2C), 125.5 (q, J_{C-F} = 4.0 Hz, 2C), 123.7 (q, J_{C-F} = 272 Hz, 1C), 118.1 (2C), 76.3 ppm.

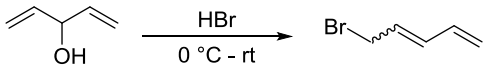
^{19}F NMR (376.5 MHz, $CDCl_3$) δ -63.00 (s, 3F) ppm.

HRMS (APPI) calcd. for [$C_{13}H_{11}O_2F_3]^+$: 256.0711, found: 256.0706.


8.20
8.18
7.72
7.70
6.01
5.99
5.98
5.97
5.96
5.94
5.93
5.92
5.44
5.43
5.42
5.40
5.39
5.38
5.32
5.30
O
O
CF3
4.6d
Chemical Shift (ppm)


164.38
135.09
134.79
134.54
134.44
134.11
133.65
130.17
129.88
127.81
125.60
125.56
125.52
125.48
125.09
122.38
119.67
118.14
76.34
O
O
CF3
4.6d
Chemical Shift (ppm)





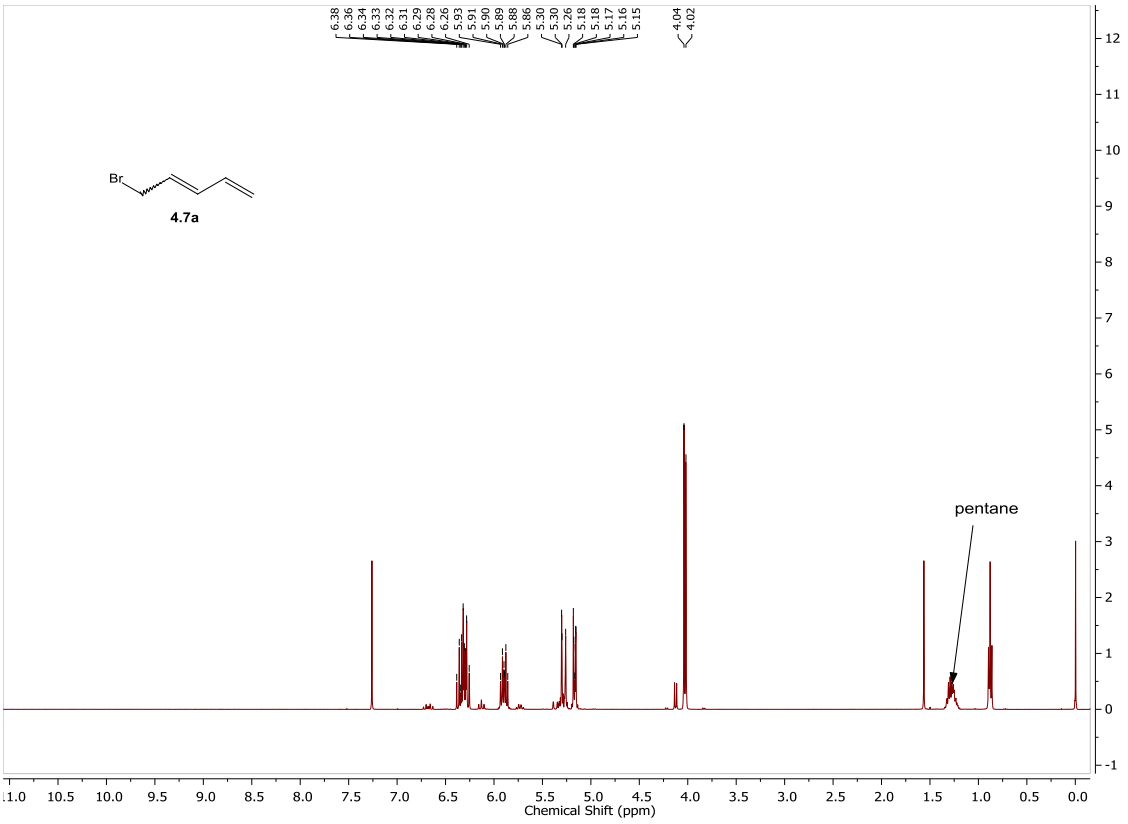
4.6e **4.7a**

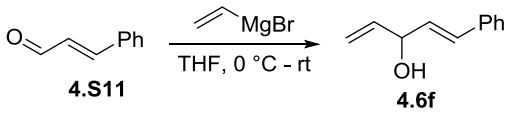
(*E*)-5-bromo-1,3-diene, 4.7a

To a stirred solution of 1,4-pentadien-3-ol **4.6e** (0.50 mL, 5.1 mmol) in pentane (0.4 mL) at 0 °C, was added HBr (0.5 mL, 9.2 mmol, 48%) dropwise. After stirring for 4 hours the reaction mixture was diluted with diethyl ether, quenched with a saturated, aqueous sodium bicarbonate solution, extracted with diethyl ether and dried over Na_2SO_4. The solution was concentrated and purified via silica gel chromatography (pentane) to give **4.7a** (200 mg, 28%) as a colorless liquid. R_f = 0.90 (80:20, hexanes/EtOAc). The

product is a mixture of two diastereomers in a 10:1 ratio. Only the major, *E* diastereomer, was fully characterized. ^{1}H and ^{13}C NMR are consistent with literature reports.[47]

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.38 – 6.26 (m, 2H), 5.89 (dt, J_d = 13.6, J_t = 7.8 Hz, 1H), 5.30 – 5.26 (m, 1H), 5.17 (dd, *J* = 9.3, 1.7 Hz, 1H), 4.03 (d, *J* = 8.0 Hz, 2H) ppm.





4.S11 **4.6f**

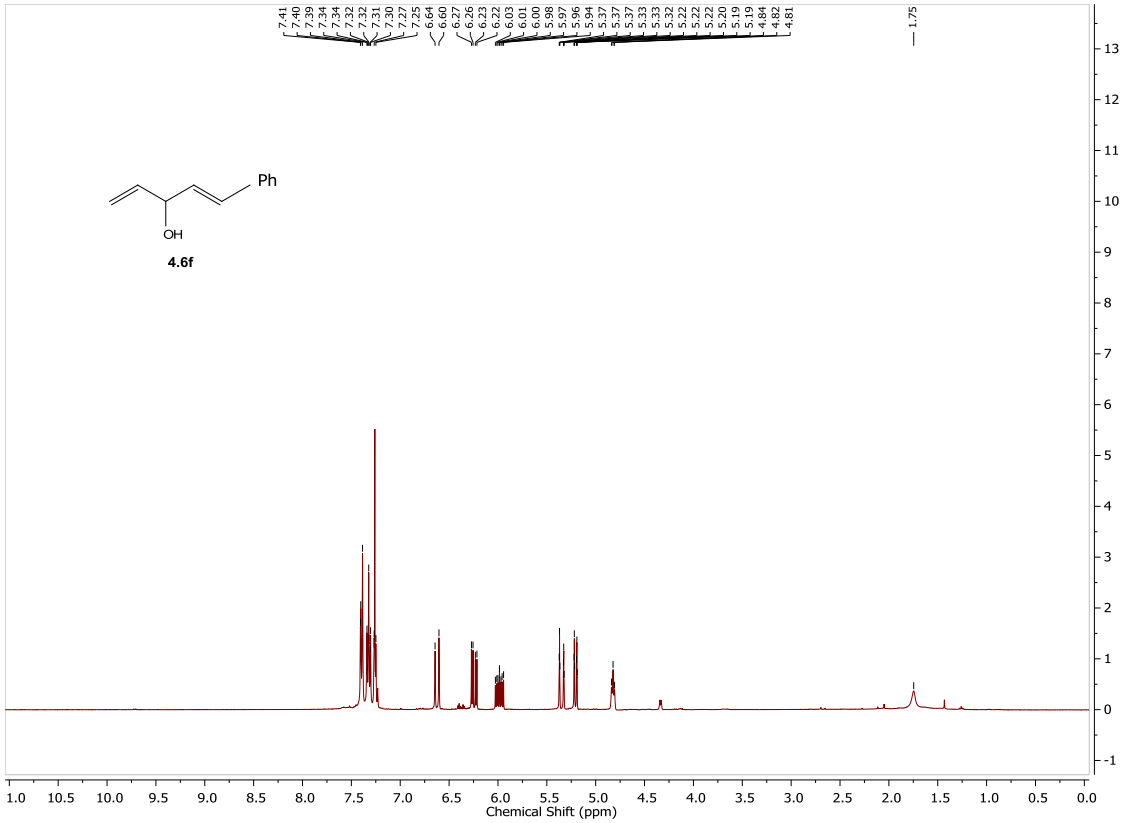
(1*E*)-1-phenylpenta-1,4-dien-3-ol, 4.6f

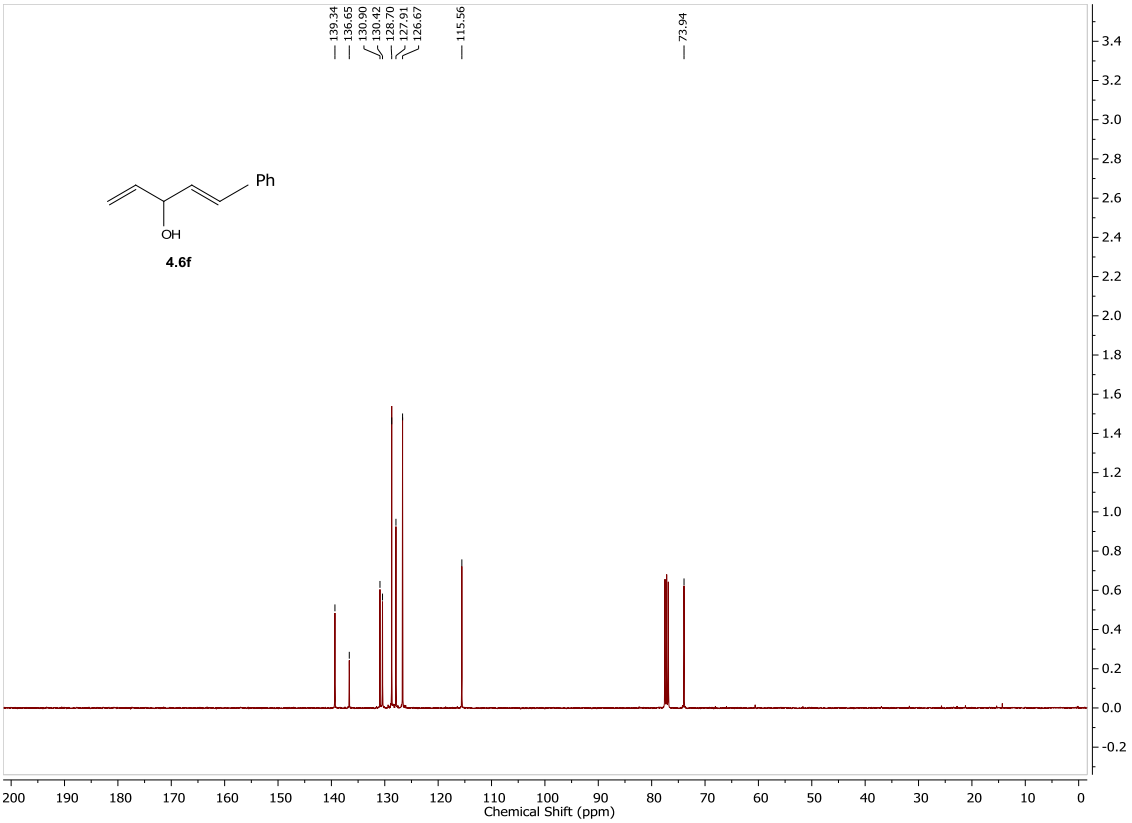
Vinyl magnesium bromide (0.7 M in THF, 13 mL, 9.1 mmol) was added dropwise to a precooled solution of *trans*-cinnamaldehyde **4.S11** (0.95 ml, 7.6 mmol) in THF (10

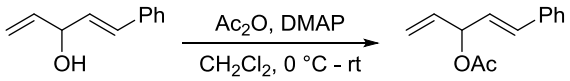
mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 4 hours before it was quenched with saturated NH_4Cl solution and extracted with ethyl acetate. The organic layers were combined, dried using $MgSO_4$, and filtered. The solution was concentrated and purified via silica gel chromatography (80:20, hexanes/EtOAc) which yielded alcohol **4.6f** (938 mg, 86%) as a yellow oil. R_f = 0.26 (80:20, hexanes/EtOAc). ^{1}H and ^{13}C NMR are consistent with literature reports.[48]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.39 (m, 2H), 7.34 – 7.30 (m, 2H), 7.25 (t, *J* = 7.0 Hz, 1H), 6.62 (d, *J* = 16.0 Hz, 1H), 6.24 (dd, *J* = 16.0, 6.4 Hz, 1H), 5.98 (ddd, *J* = 16.8, 10.5, 5.9 Hz, 1H), 5.35 (dt, J_d = 17.5, J_t = 1.4 Hz, 1H), 5.21 (dt, J_d = 10.3, J_t = 1.1 Hz, 1H), 4.82 (t, *J* = 6.4 Hz, 1H), 1.75 (bs, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 139.3, 136.7, 130.9, 130.4, 128.7 (2C), 127.9, 126.7 (2C), 115.6, 73.9 ppm.


7.41
7.40
7.39
7.34
7.34
7.32
7.32
7.31
7.30
7.27
7.25
6.64
6.60
6.27
6.26
6.23
6.22
6.03
6.01
6.00
5.98
5.97
5.96
5.94
5.37
5.37
5.37
5.33
5.33
5.32
5.22
5.22
5.20
5.19
5.19
4.84
4.82
4.81
1.75
Ph
OH
4.6f
Chemical Shift (ppm)





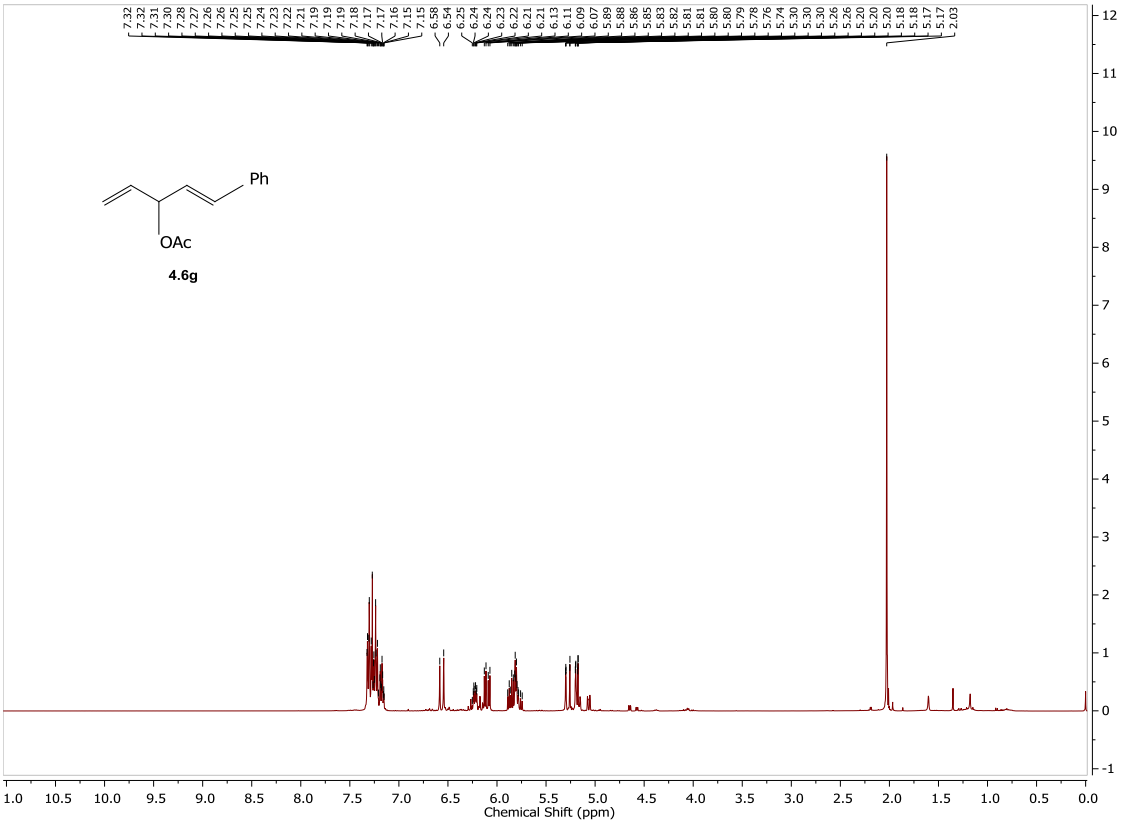
4.6f **4.6g**

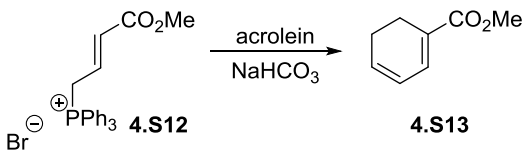
(*E*)-1-phenylpenta-1,4-dien-3-yl acetate, 4.6g

Acetic anhydride (0.45 mL, 4.3 mmol) was added dropwise to a solution of DMAP (0.95 g, 0.78 mmol) and (*E*)-1-phenylpenta-1,4-dien-3-ol **4.6f** (0.55 g, 3.5 mmol) in CH_2Cl_2 (7.1 mL) at 0 ºC. The reaction mixture was allowed to warm to room temperature and stirred for 24 hours before it was concentrated under reduced pressure and purified via silica gel chromatography (97:3, hexanes/EtOAc) to yield acetate **4.6g**

(168 mg, 53%) as a yellow oil. R_f = 0.56 (97:3, hexanes/EtOAc). ^{1}H and ^{13}C NMR are consistent with literature reports.[49]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.21 (m, 3H), 7.19 – 7.15 (m, 2H), 6.56 (d, *J* = 16.0 Hz, 1H), 6.25 – 6.12 (m, 1H), 6.10 (dd, *J* = 16.0, 6.8 Hz, 1H), 5.89 – 5.74 (m, 1H), 5.30 – 5.26 (m, 1H), 5.20 – 5.17 (m, 1H), 2.03 (s, 3H) ppm.

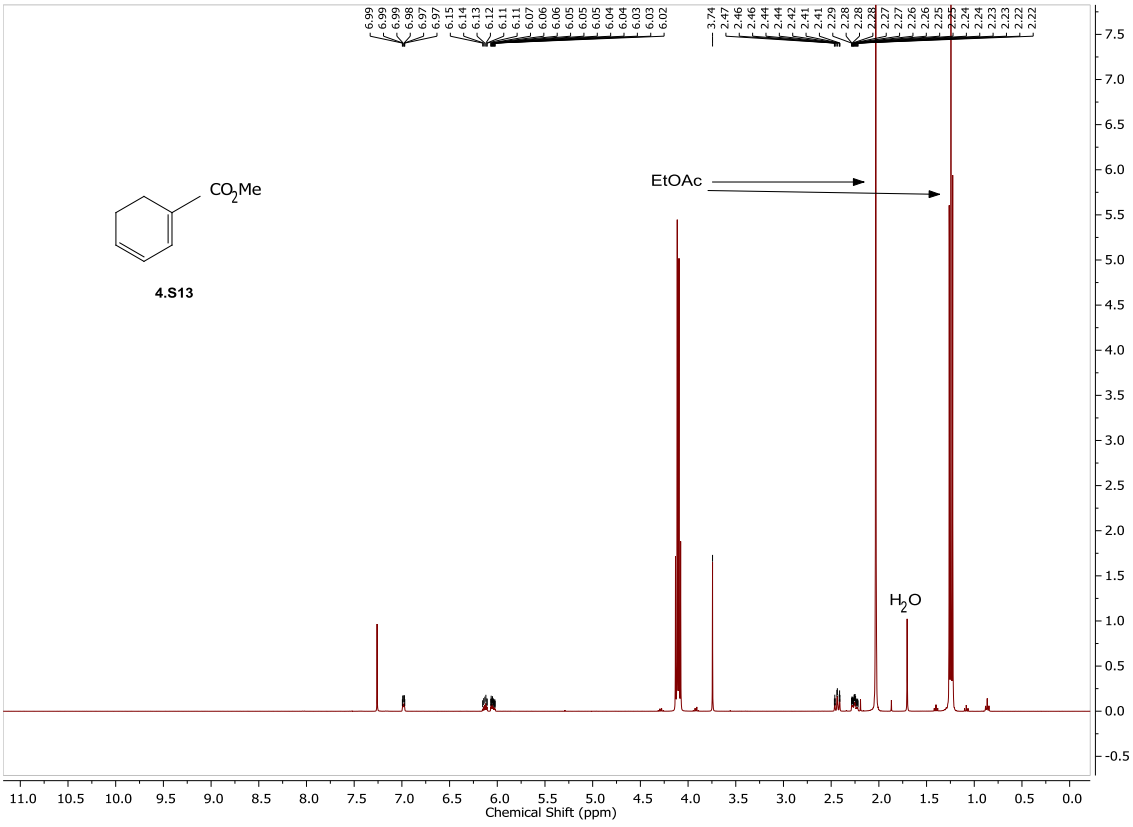


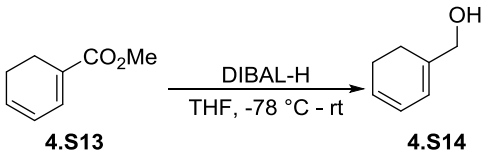


Methyl cyclohexa-1,3-diene-1-carboxylate, 4.S13

Following a previously reported procedure, ester **4.S13**[41] was synthesized as a colorless oil, (350 mg, 30%). R_f = 0.38 (75:25, hexanes/EtOAc). ^{1}H and ^{13}C NMR are consistent with literature reports.[41] This compound was prone to air oxidation to methyl benzoate so it was moved forward synthetically prior to complete removal of solvent.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 – 6.96 (m, 1H), 6.13 (dt, J_d = 8.6, J_t = 4.3 Hz, 1H), 6.05 (ddt, J_d = 9.5, 5.5, J_t = 1.8 Hz, 1H), 3.74 (s, 3H), 2.48 – 2.37 (m, 2H), 2.29 – 2.21 (m, 2H) ppm.



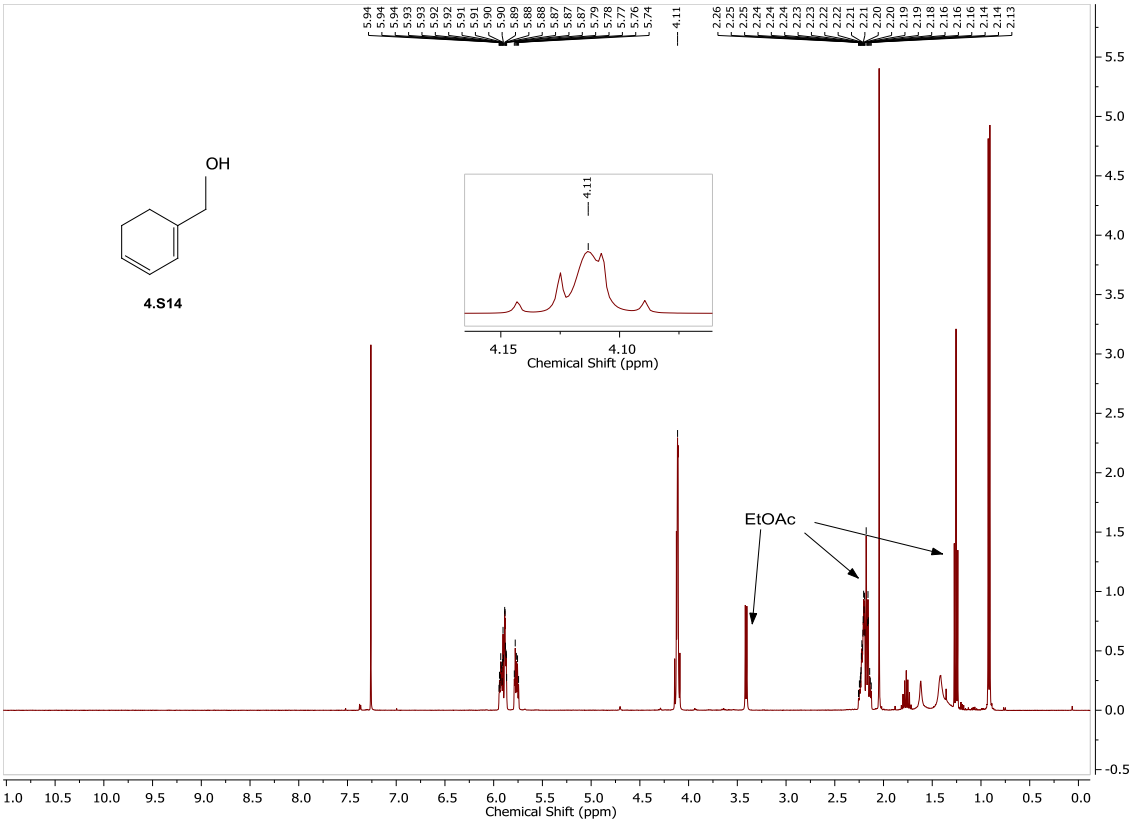


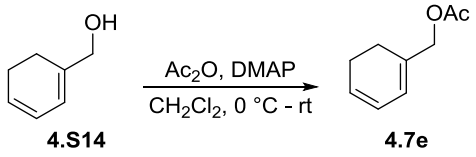
4.S13 **4.S14**

1,3-cyclohexadiene-1-methanol, 4.S14

DIBAL-H in toluene (1.2 M, 4.1 mL, 5.0 mmol) was added to ester **4.S13** (350 mg, 2.5 mmol) in THF (10 mL) at -78 ºC. The reaction was allowed to warm to room temperature and stirred overnight. The reaction mixture was filtered through Celite®, acidified with 10% aqueous HCl, extracted with diethyl ether, and dried using Na_2SO_4. The solution was concentrated and purified via silica gel chromatography (80:20, hexanes/EtOAc) to give (274 mg, 99%) of alcohol **4.S14**. R_f = 0.19 (80:20, hexanes/EtOAc). ^{1}H and ^{13}C NMR are consistent with literature reports.[50] This compound was prone to air oxidation to benzyl alcohol so it was moved forward synthetically prior to complete removal of solvent.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.94 – 5.87 (m, 2H), 5.77 (dt, J_d = 9.0, J_t = 4.0 Hz, 1H), 4.11 (s, 2H), 3.4 (s, O*H*), 2.26 – 2.13 (m, 4H) ppm.





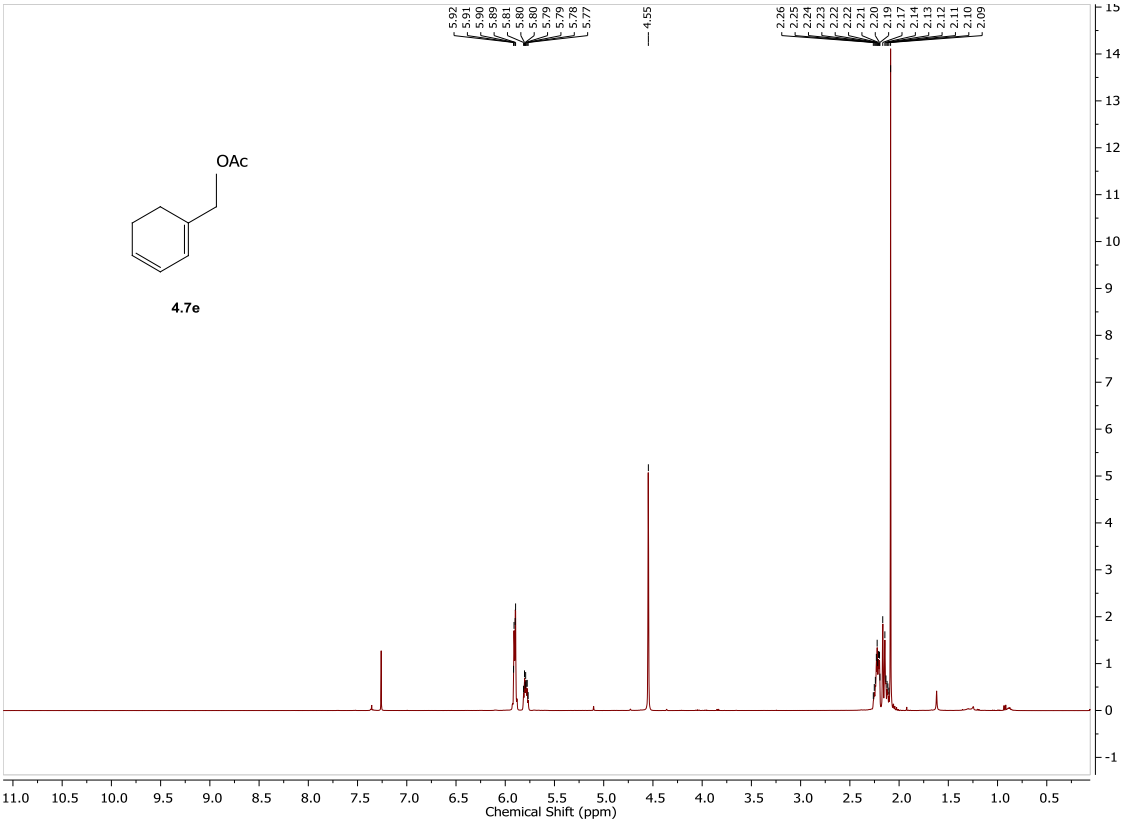
Cyclohexa-1,3-dien-1-ylmethyl acetate, 4.7e

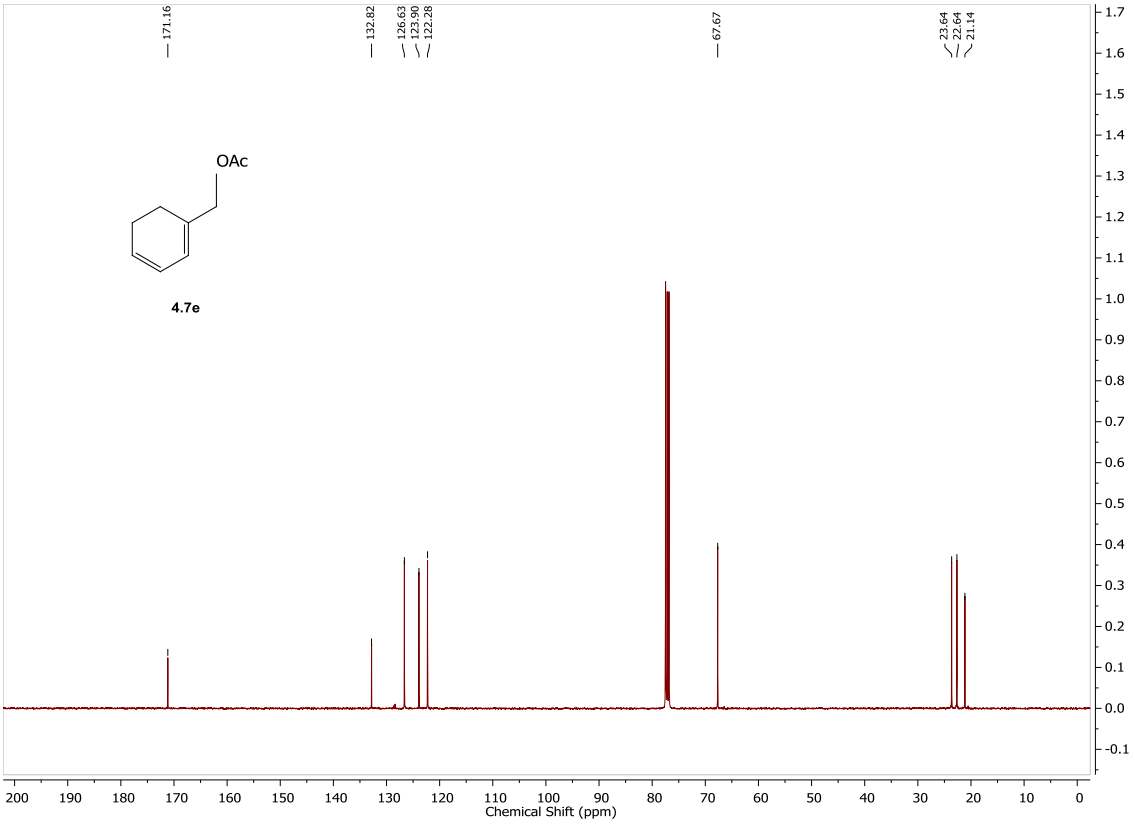
To a solution of alcohol **4.S14** (274 mg, 2.5 mmol) in CH_2Cl_2 (25 mL) was added acetic anhydride (0.25 mL, 2.5 mmol) and DMAP (61 mg, 0.5 mmol) at 0 °C. After stirring for 18 hours at room temperature, the reaction was diluted with CH_2Cl_2 and washed with water. The aqueous layer was back extracted with CH_2Cl_2, and the combined organic layers were dried using Na_2SO_4 and concentrated to give acetate **4.7e**

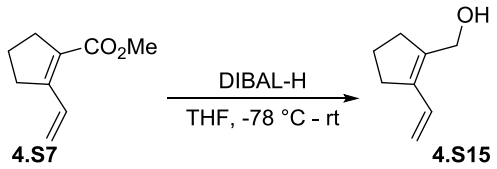
(171 mg, 45%) as a yellow liquid. R_f = 0.65 (90:10, hexanes/EtOAc). Due to the instability, HRMS data was not obtained.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.92 – 5.89 (m, 2H), 5.81 – 5.77(m, 1H), 4.55 (s, 2H), 2.25 – 2.10 (m, 4H), 2.09 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 132.8, 126.6, 123.9, 122.2, 67.7, 23.6, 22.6, 21.1 ppm.







(2-vinylcyclopent-1-en-1-yl)methanol, 4.S15

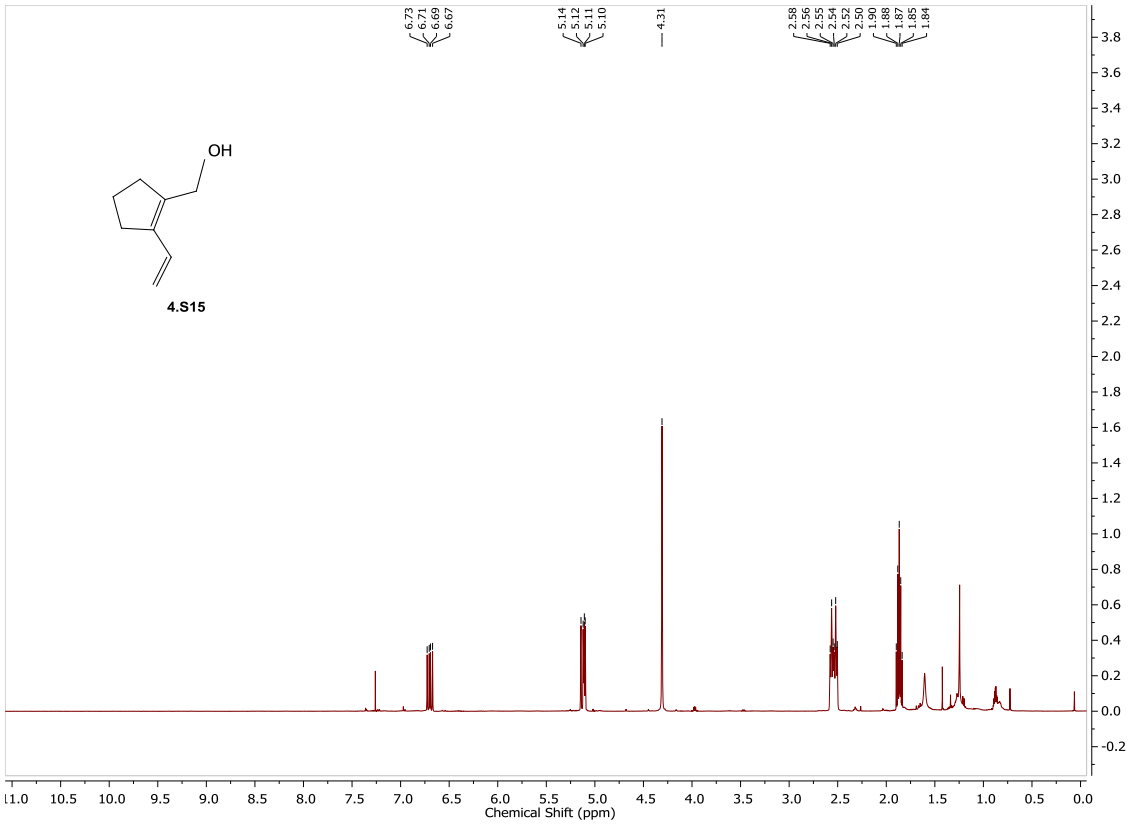
DIBAL-H in toluene (1.2 M, 1.0 mL, 1.2 mmol) was added to ester **4.S7** (88 mg, 0.58 mmol) in THF (5.8 mL) at -78 ºC. The reaction was warmed to room temperature. After stirring for 4 hours the reaction mixture was quenched first with $Na_2SO_4 \cdot 10H_2O$ until bubbling ceased and then with saturated NH_4Cl solution, extracted with diethyl ether, and dried using Na_2SO_4. The solution was concentrated and purified via silica gel

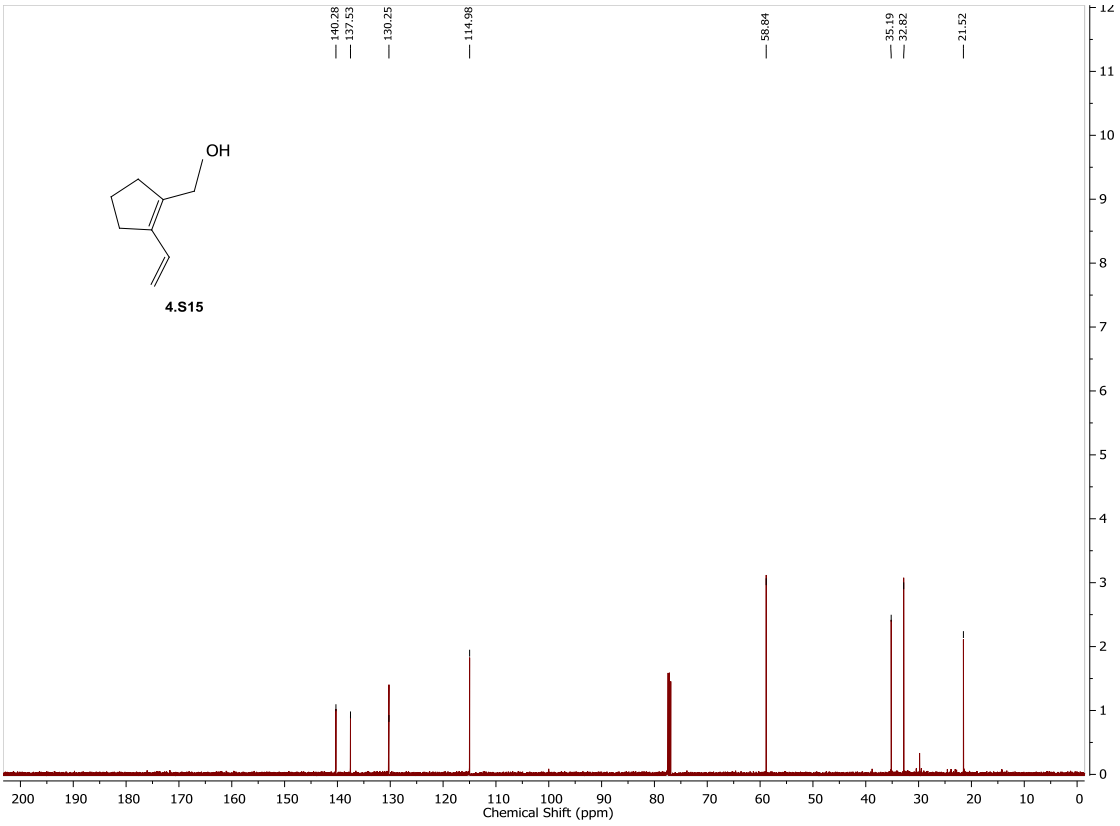
chromatography (80:20, pentane/diethyl ether) to give alcohol **4.S15** (53 mg, 75%) as a yellow oil. R_f = 0.31 (80:20, hexanes/EtOAc).

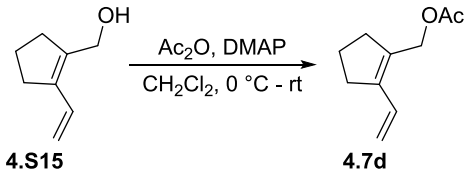
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.70 (dd, *J* = 17.2, 10.7 Hz, 1H), 5.14 – 5.10 (m, 2H), 4.31 (s, 2H), 2.56 (t, *J* = 7.4 Hz, 2H), 2.52 (t, *J* = 7.6 Hz, 2H), 1.87 (quint, *J* = 7.5 Hz, 2H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ 140.3, 137.5, 130.3, 115.0, 58.8, 35.2, 32.8, 21.5 ppm.

HRMS (ESI) calcd. for $[C_8H_{12}O+H]^+$: 125.0966, found: 125.0961.


6.73
6.71
6.69
6.67
5.14
5.12
5.11
5.10
4.31
2.58
2.56
2.55
2.54
2.52
2.50
1.90
1.88
1.87
1.85
1.84
OH
4.S15
Chemical Shift (ppm)





(2-vinylcyclopent-1-en-1-yl)methyl acetate, 4.7d

To a solution of alcohol **4.S15** (20 mg, 0.16 mmol) and triethylamine (45µL, 0.32 mmol) in CH_2Cl_2 (1.6 mL) was added acetic anhydride (19 µL, 0.19 mmol) and DMAP (2.0 mg, 0.016 mmol) at 0 °C. After stirring for an hour at room temperature, the reaction was diluted with diethyl ether and washed with water. The aqueous layer was back extracted with diethyl ether, and the combined organic layers dried using Na_2SO_4 and

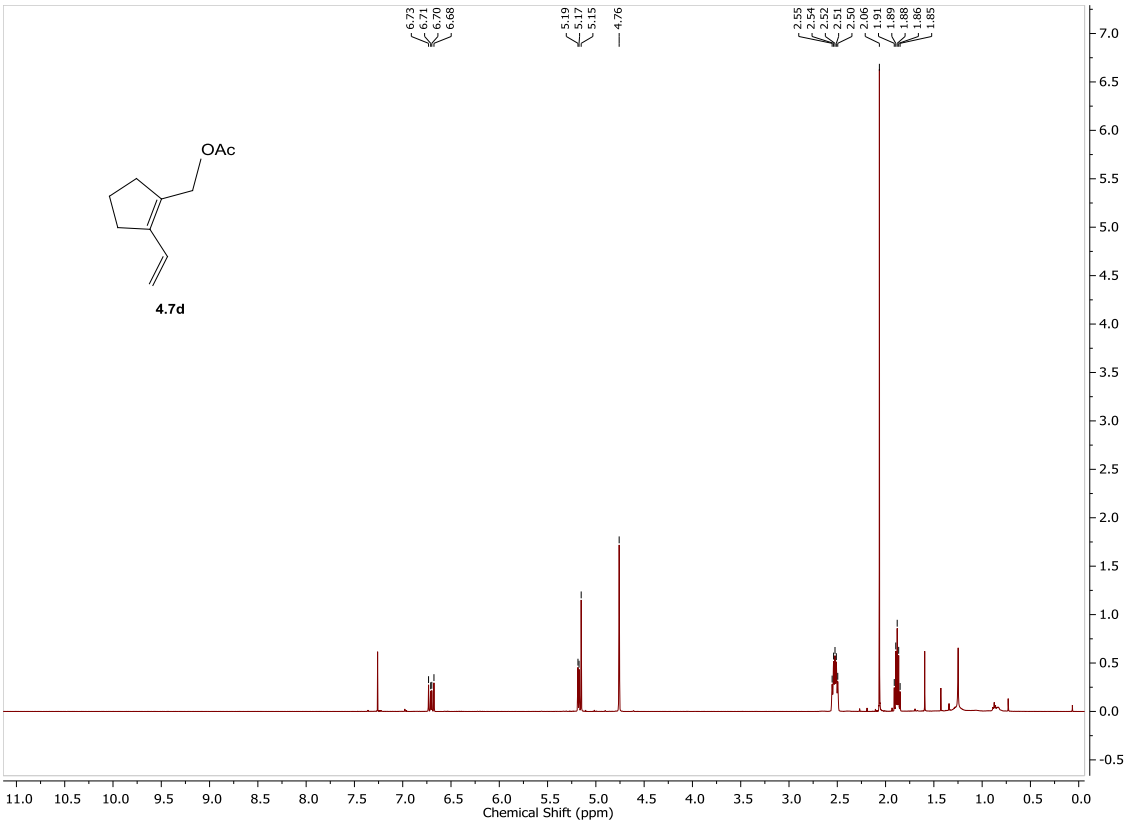
concentrated. Purification via silica gel chromatography (95:5, pentane/diethyl ether) yielded acetate **4.7d** (15 mg, 56%) as a yellow oil. R_f = 0.76 (80:20, hexanes/EtOAc).

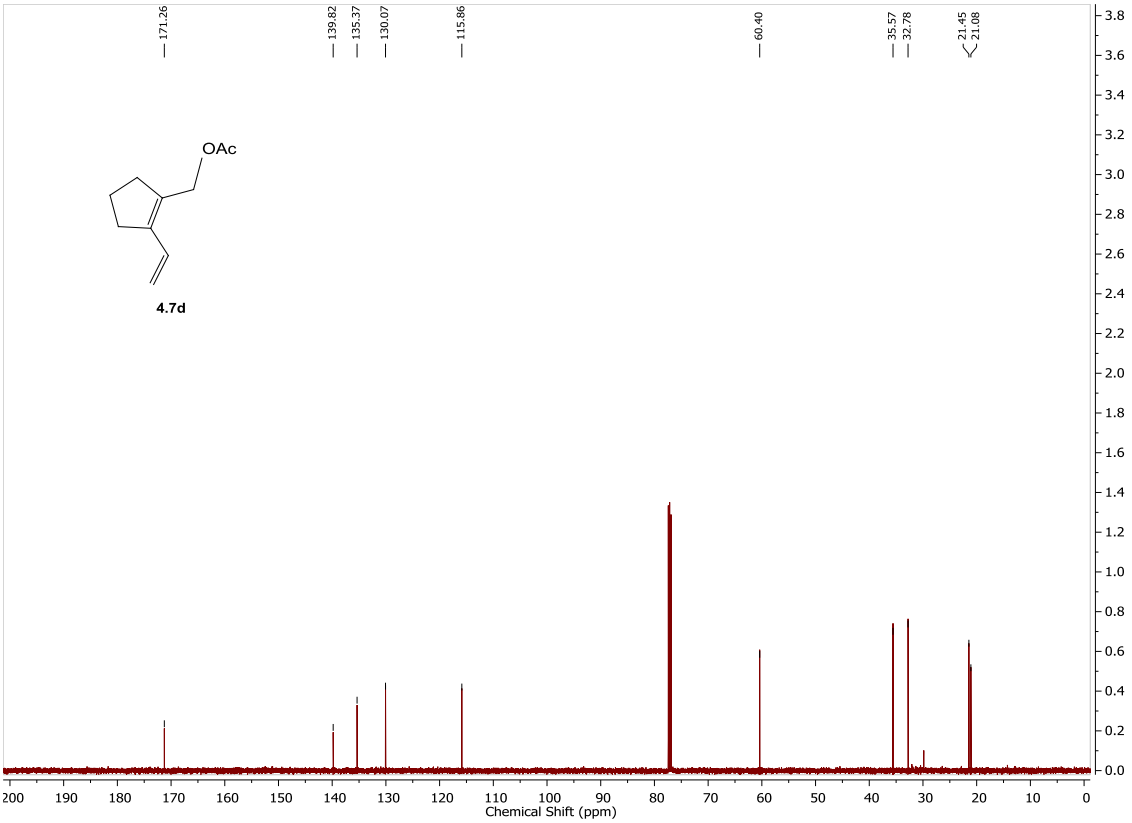
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.70 (dd, *J* = 16.8, 11.1 Hz, 1H), 5.17 (d, *J* = 16.7 Hz, 1H), 5.16 (d, 11.0 Hz, 1H), 4.76 (s, 2H), 2.55 – 2.50 (m, 4H), 2.06 (s, 3H), 1.88 (quint, *J* = 7.6 Hz, 2H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ 171.2, 139.8, 135.3, 130.0, 115.8, 60.4, 35.5, 32.7, 21.4, 21.0 ppm.

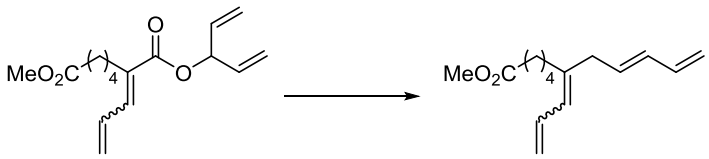
GC-LR-MS (EI 70 eV) m/z (%) calcd. for $[C_{10}H_{14}O_2]^+$: 166, found: 166.

Attempts to obtain HRMS data using ESI and API were unsuccessful.


6.73
6.71
6.70
6.68
5.19
5.17
5.15
4.76
2.55
2.54
2.52
2.51
2.50
2.06
1.91
1.89
1.88
1.86
1.85
OAc
4.7d
Chemical Shift (ppm)



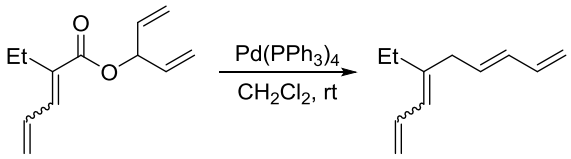
4.6 Experimental Procedures for Single Component Decarboxylative Coupling



4.9 **4.10**

(6*E*/*Z*,8*E*)-methyl 6-allylideneundeca-8,10-dienoate, 4.10

See Chapter III-section 3.2.1, page 79 compound **3.9** for experimental details,



4.11 **4.12**

(6*E*)-4-ethylnona-1,3,6,8-tetraene, 4.12

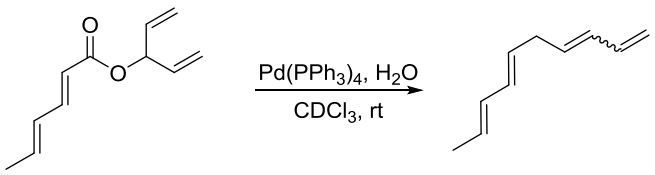
Dienoate **4.11** (40 mg, 0.17 mmol)[39] was added to a small vial with CH_2Cl_2 (2 mL) after which tetrakis-(triphenylphosphine) palladium (19.7 mg, 0.017 mmol) was added. The vial was sealed and purged with N_2. When initially prepared, the solution was a dark orange color, but after 24 hours, it was a light yellow color. At this time, the reaction was concentrated and purified via silica gel chromatography (hexanes) to yield ethyl tetraene **4.12**. The yield was inconsistent due to the extreme volatility of the product which made removing solvent difficult.[39]

Diastereomer A:

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18 (d, *J* = 11.5 Hz, 1H), 6.68 (ddd, *J* = 10.3, 11.3, 16.8 Hz, 1H), 5.89 (ddd, *J* = 5.8, 10.3, 16.6 Hz, 2H), 5.84 – 5.78 (m, 1H), 5.59 (dd, *J* = 1.1, 16.6 Hz, 1H), 5.47 (dd, *J* = 1.1, 10.3 Hz, 1H), 5.37 – 5.31 (m, 2H), 5.27 – 5.23 (m, 2H), 2.46 (q, *J* = 7.4 Hz, 2H), 1.06 (t, *J* = 7.4 Hz, 3H) ppm.

Diastereomer B:

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.22 (m, 1H), 6.38 (d, *J* = 11.5 Hz, 1H), 5.89 (ddd, *J* = 5.8, 10.3, 16.6 Hz, 2H), 5.84 – 5.78 (m, 1H), 5.40 (dd, *J* = 1.7, 17.1 Hz, 1H), 5.37 – 5.31 (m, 3H), 5.27 – 5.23 (m, 2H), 2.38 (q, *J* = 7.4 Hz, 2H), 1.09 (t, *J* = 7.5 Hz, 3H) ppm.



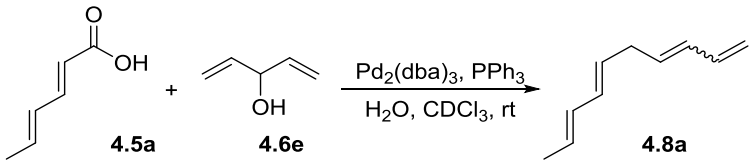
4.13 **4.8a**

(6*E*,8*E*)-deca-1,3,6,8-tetraene, 4.8a

To a microwave vial with dienoate **4.13** (11 mg, 0.063 mmol) and water (1.25 µL, 0.07 mmol) in $CDCl_3$ (1.5 mL) was added tetrakis-(triphenylphosphine) palladium (7.3 mg, 0.0063 mmol) and the vial was sealed and purged with N_2. The mixture was stirred at room temperature for 24 hours and then transferred to a vial containing dimethylterphthalate (2.6 mg, internal standard). Quantitative ^{1}H NMR analysis of this mixture shows the formation of tetraene **4.8a** (5%) in addition to the rearranged ester **4.20**. The spectral data for (6*E*,8*E*)-deca-1,3,6,8-tetraene, **4.8a** is provided below for the two component reaction.

4.7 Experimental Procedures for Two Component Decarboxylative Coupling

***General Procedure*:** A microwave vial with dienoic acid **4.5** (1.0 eq), pentadienyl substrate **4.6** (1.2 eq) and water (1.1 eq) in $CDCl_3$ (0.1 M) was capped with a septum, and purged with N_2. Tris(dibenzylideneacetone)dipalladium(0)-chloroform adduct (5 mol %) and PPh_3 (20%) were dissolved in $CDCl_3$ (0.1 mL) and added to the mixture. The mixture was left at room temperature under a balloon of N_2 for 48 hours. The solution was concentrated and purified via silica gel chromatography using pentane.



(6*E*,8*E*)-deca-1,3,6,8-tetraene, 4.8a

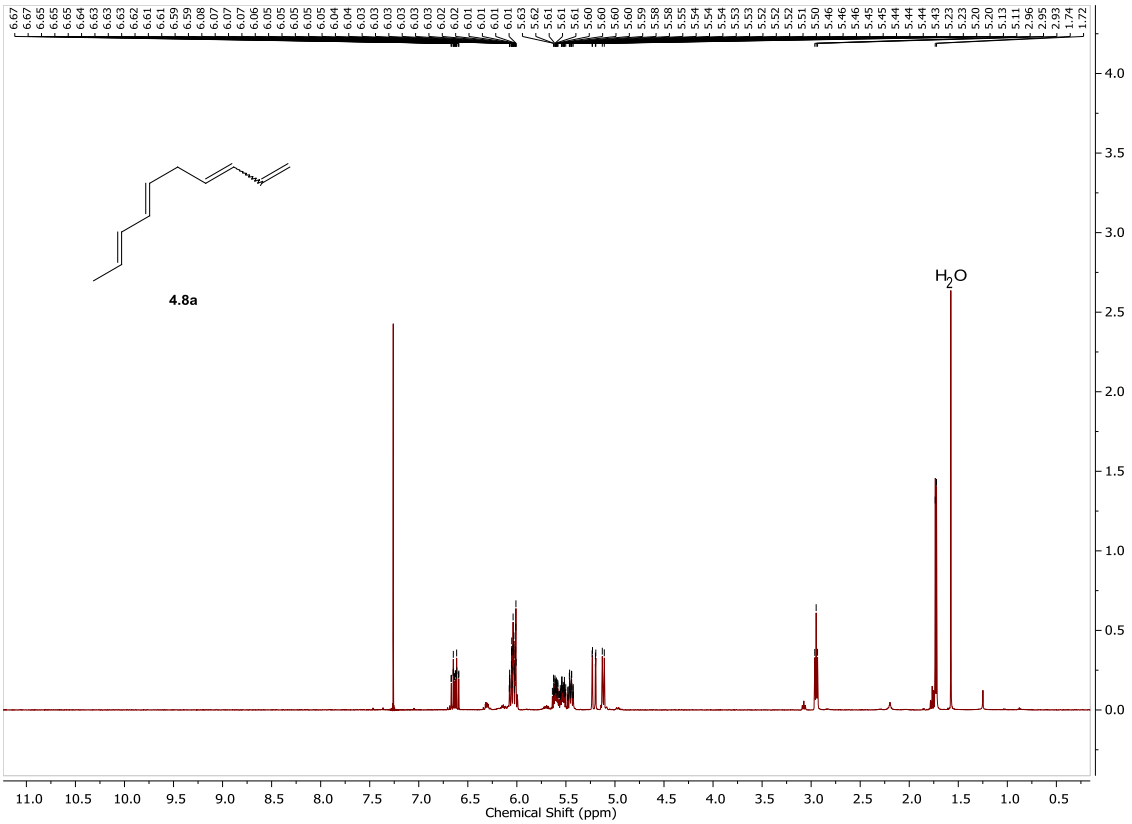
Following the general procedure, tetraene **4.8a** was synthesized as a colorless solution in $CDCl_3$ (40% ^{1}H NMR yield). R_f (mixture of diastereomers) = 0.78 (hexanes). The product is a mixture of two diastereomers in a 10:1 ratio. Only the major, all-*E* diastereomer, was fully characterized.

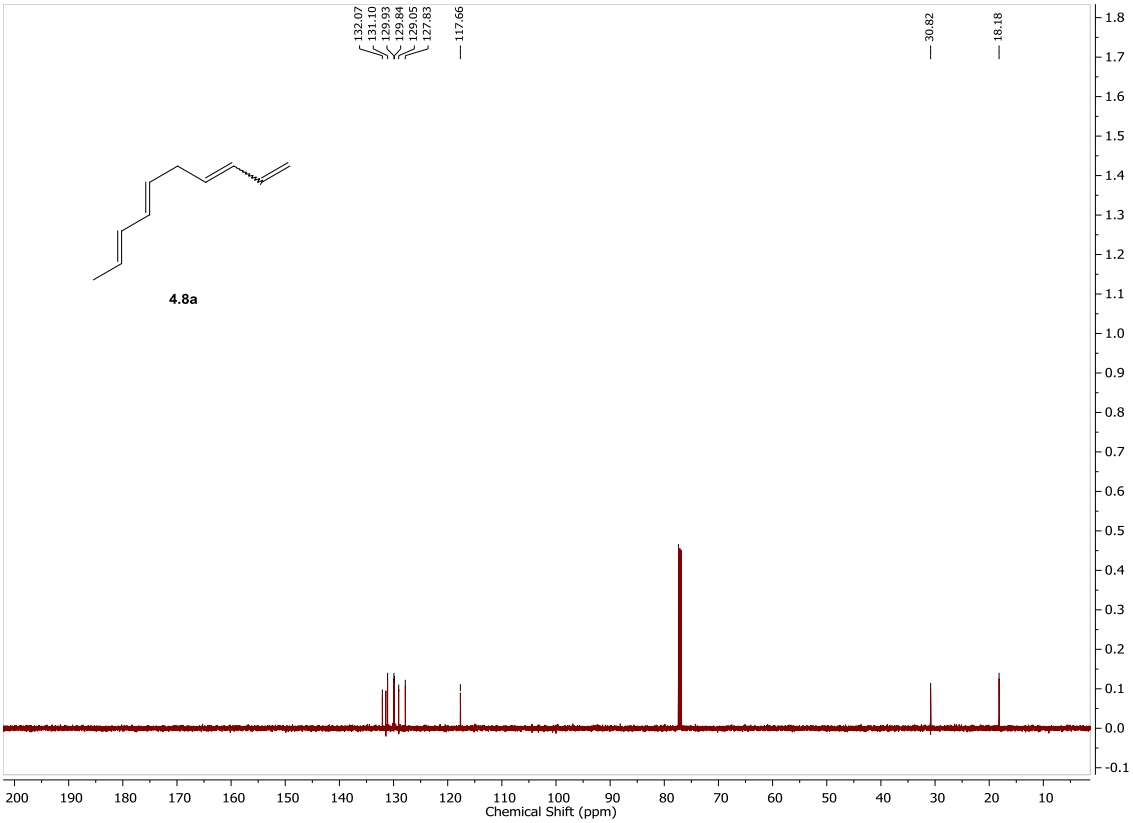
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.63 (dddd, *J* = 16.9, 11.2, 10.2, 1.1 Hz, 1H), 6.07 – 5.99 (m, 3H), 5.64 – 5.58 (m, 1H), 5.57 – 5.50 (m, 1H), 5.47 – 5.42 (m, 1H), 5.23 (dd, *J* = 16.8, 2.0 Hz, 1H), 5.12 (d, *J* = 10.2 Hz, 1H), 3.07 (t, *J* = 7.5 Hz, C*H*$_2$ *minor isomer*), 2.95 (t, *J* = 7.1 Hz, 2H), 1.73 (d, *J* = 6.0 Hz, 3H) ppm.

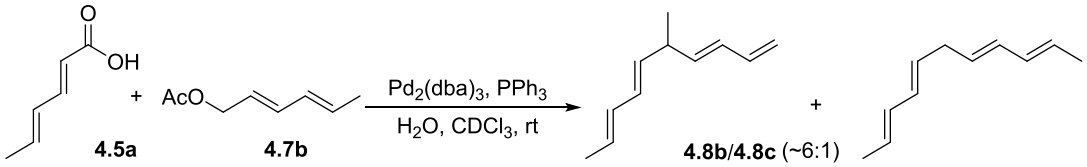
^{13}C NMR (125 MHz, $CDCl_3$) δ 132.1, 131.4, 131.1, 129.9, 129.8, 129.1, 127.8, 117.7, 30.8, 18.2 ppm.

GC-LR-MS (EI 70 eV) m/z (%) calcd. for $C_{10}H_{14}$: 134, found: 134.

Attempts to obtain HRMS data using ESI and API were unsuccessful.


4.8a
H2O
Chemical Shift (ppm)





5-methyldeca-1,3,6,8-tetraene, 4.8b

Following the general procedure, tetraene **4.8b** was synthesized as a colorless oil (3.4 mg, 8% yield). R_f = 0.63 (hexanes). The product is a mixture of two isomers **4.8b/4.8c** in a 6:1 ratio. Only the major isomer **4.8b** was fully characterized.

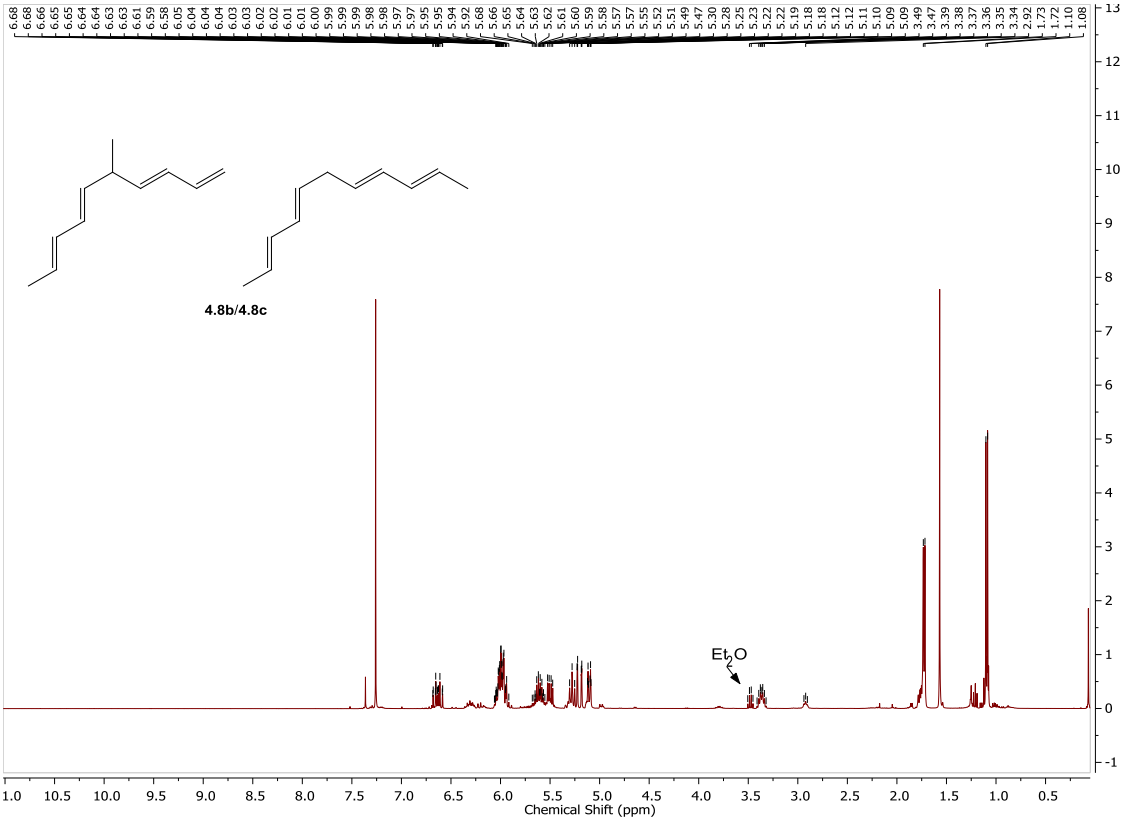
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.68 – 6.58 (m, 1H), 6.06 – 5.92 (m, 3H), 5.68 – 5.55 (m, 1H), 5.49 (dd, *J* = 14.3, 6.3 Hz, 1H), 5.27 (t, *J* = 10 Hz, 1H), 5.19 (dd, *J* = 16.8, 1.9 Hz,

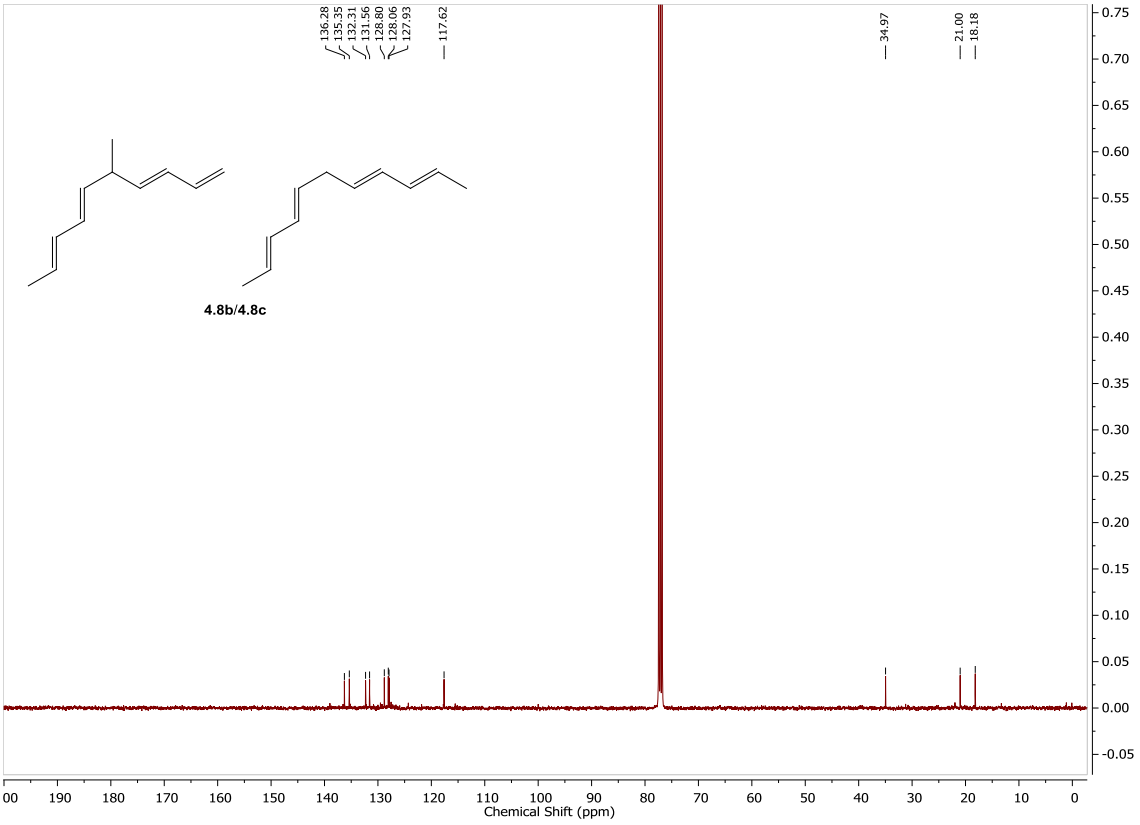
1H), 5.10 (td, J_d = 9.9, J_t = 2.0 Hz, 1H), 3.35 (dq, J_q = 16.0, J_d = 6.8, 1H), 2.91 (t, J = 6.7 Hz, CH_2 *minor isomer* **4.8c**), 1.73 (d, J = 6.6 Hz, 3H), 1.08 (d, J = 6.8 Hz, 3H) ppm.

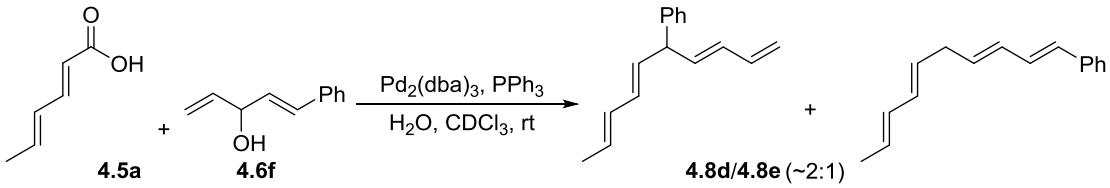
^{13}C NMR (100 MHz, $CDCl_3$) δ 136.3, 135.4, 132.3, 131.6, 128.8, 128.1, 127.9, 117.6, 34.9, 21.0, 18.2 ppm.

GC-LR-MS (EI 70 eV) m/z (%) calcd. for $C_{11}H_{16}$: 148, found: 148.

Attempts to obtain HRMS data using ESI and API were unsuccessful.







(deca-1,3,6,8-tetraen-5-yl)benzene, 4.8d

Following the general procedure, tetraene **4.8d** was synthesized as a colorless oil, (6.3 mg, 17% isolated yield). R_f = 0.37 (hexanes). The product is a mixture of two isomers **4.8d/4.8e** in a 2:1 ratio. Only the major isomer **4.8d** was fully characterized.

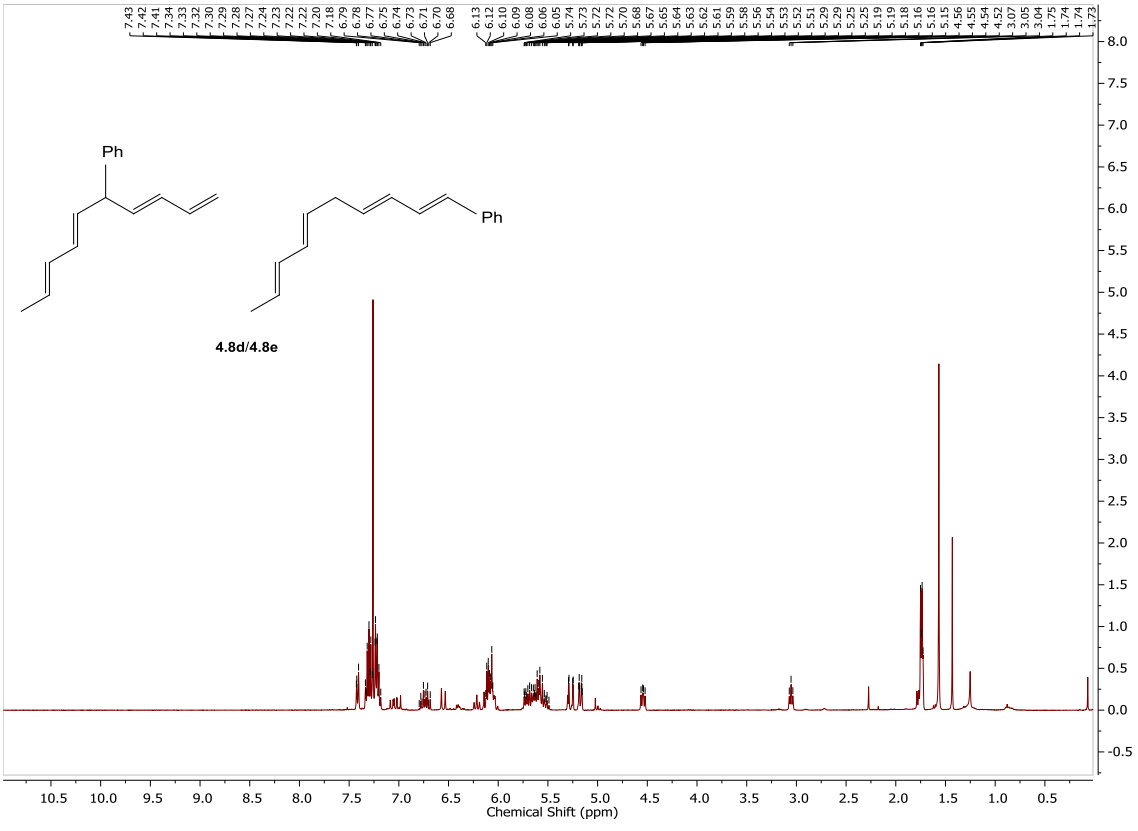
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.38 (m, 1H), 7.35 – 7.27 (m, 2H), 7.25 – 7.15 (m, 2H), 6.73 (dt, J_d = 16.9, J_t = 10.6 Hz, 1H), 6.12 – 6.04 (m, 3H), 5.74 – 5.49 (m, 3H), 5.27

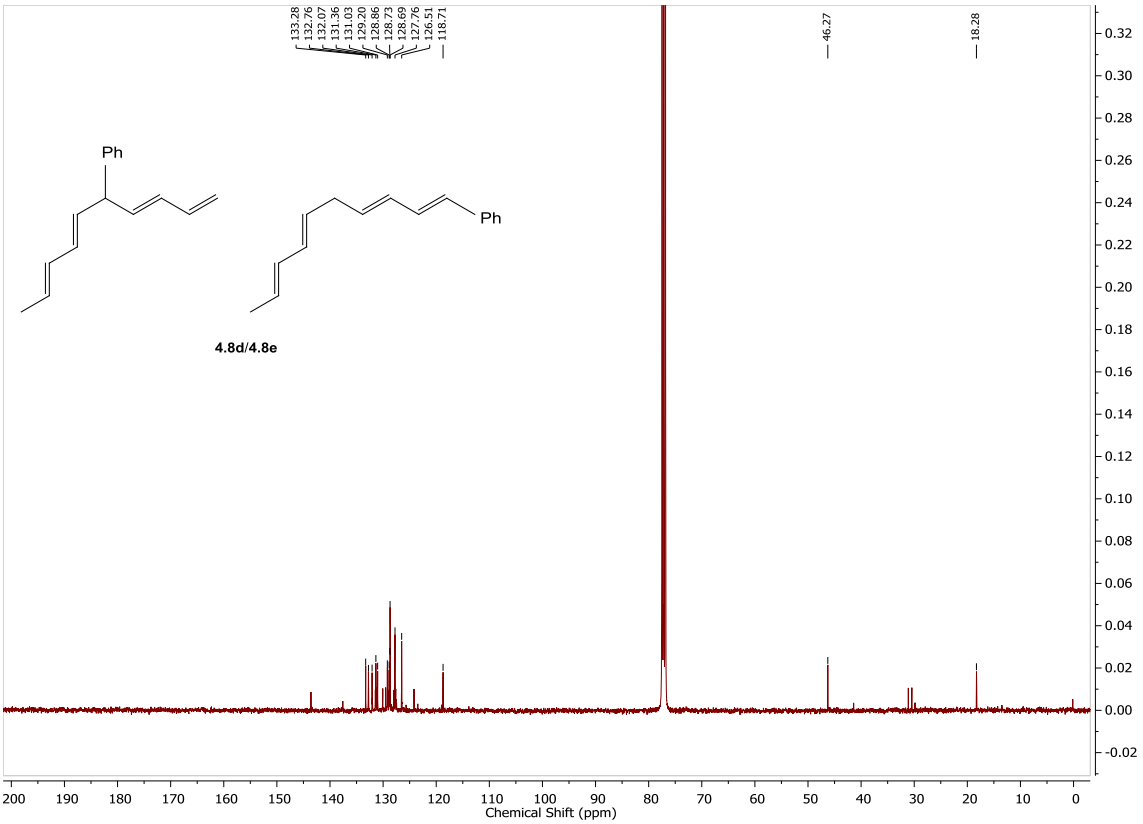
(dd, *J* = 16.9, 9.2 Hz, 1H), 5.17 (dd, *J* = 10.4, 1.9 Hz, 1H), 4.54 (dd, *J* = 9.9, 6.5 Hz, 1H, C*H benzylic* major isomer **4.8d**), 3.05 (t, *J* = 7.2 Hz, 2H, CH_2 *minor isomer* **4.8e**), 1.74 (d, *J* = 6.1 Hz, 3H, *major isomer* **4.8d**) 1.73 (d, *J* = 6.1 Hz, 3H, CH_3 *minor isomer* **4.8e**) ppm.

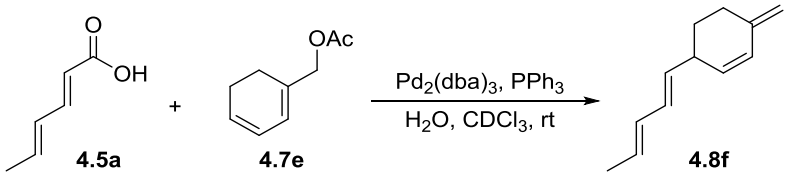
^{13}C NMR (100 MHz, $CDCl_3$) δ 133.2, 132.7, 132.0, 131.3, 131.0, 129.2, 128.8, 128.7, 128.6 (2C), 127.7 (2C), 126.5, 118.7, 46.2, 18.2 ppm.

GC-LR-MS (EI 70 eV) m/z (%) calcd. for $C_{16}H_{18}$: 210, found: 210.

Attempts to obtain HRMS data using ESI and API were unsuccessful.







3-methylene-6-((1*E*,3*E*)-penta-1,3-dien-1-yl)cyclohex-1-ene, 4.8f

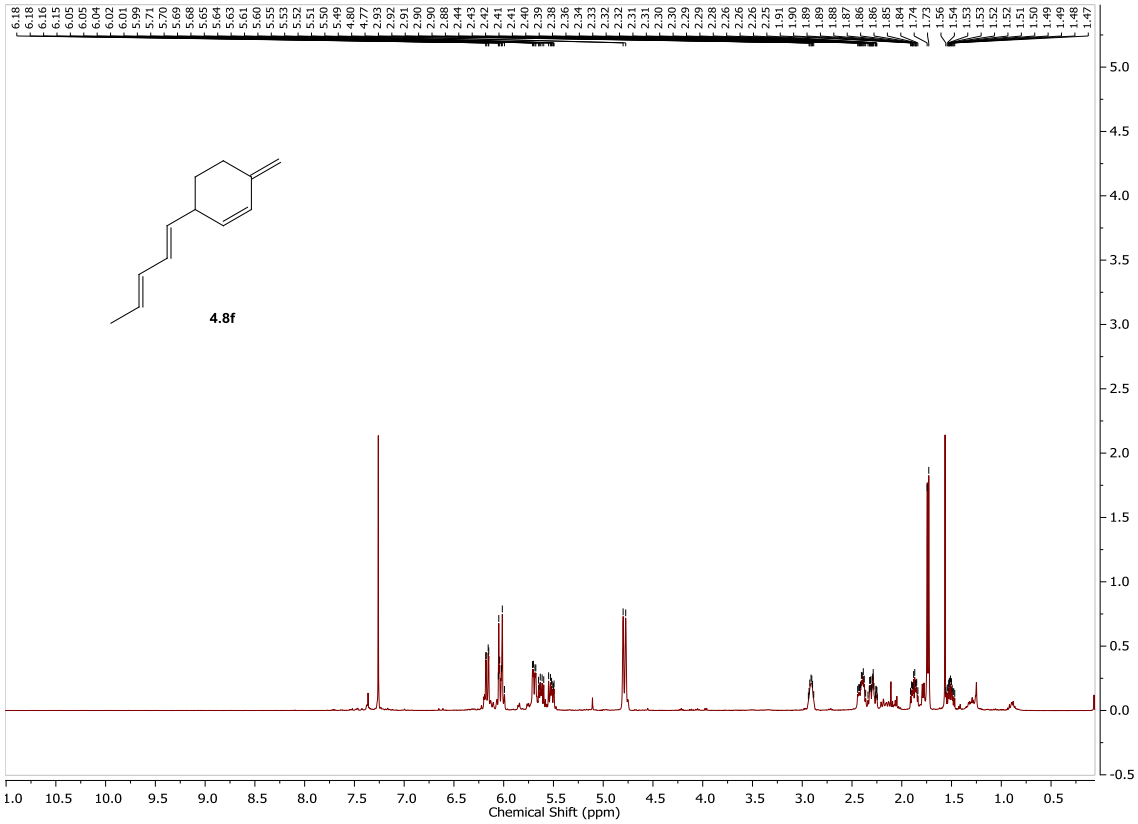
Following the general procedure, tetraene **4.8f** was synthesized as a light yellow oil, (3.5 mg, 16%). R_f = 0.96 (90:10, hexanes/EtOAc).

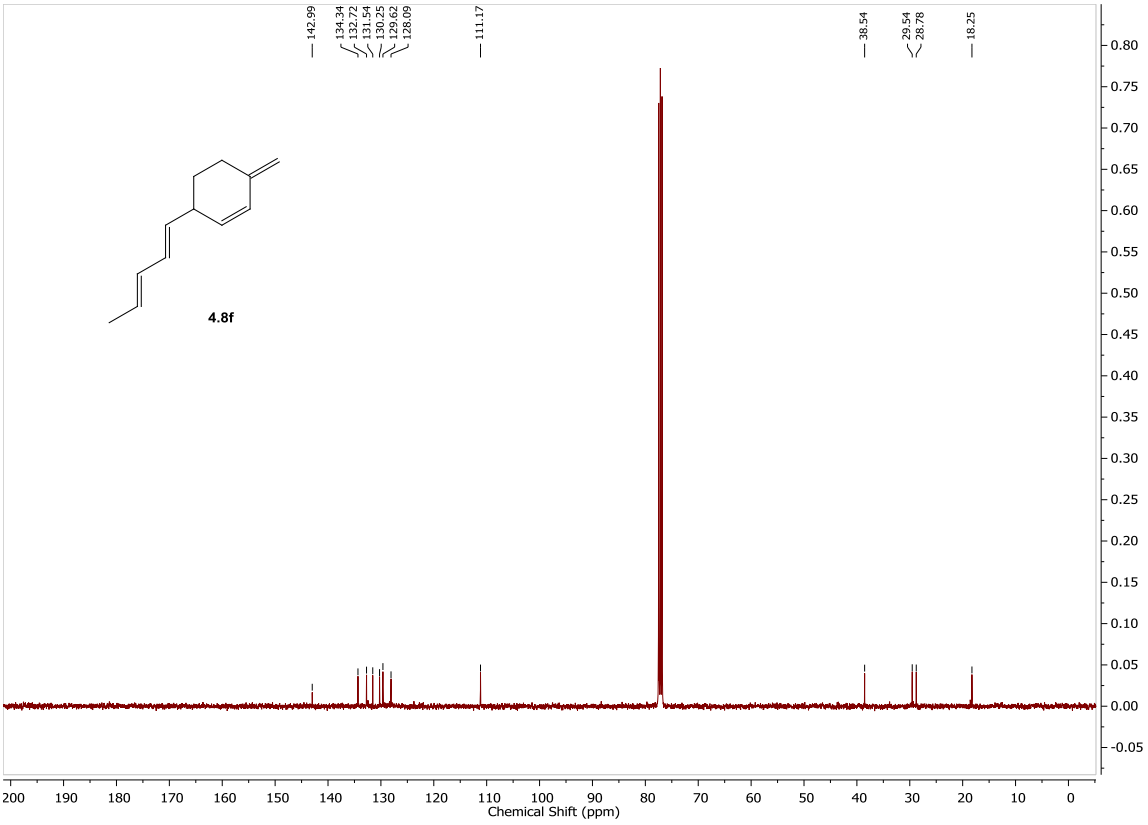
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.17 (dd, *J* = 10.0, 2.2 Hz, 1H), 6.05 – 5.99 (m, 2H), 5.69 (dd, *J* = 9.7, 3.7 Hz, 1H), 5.65 – 5.60 (m, 1H), 5.55 – 5.49 (m, 1H), 4.80 (s, 1H), 4.77 (s,

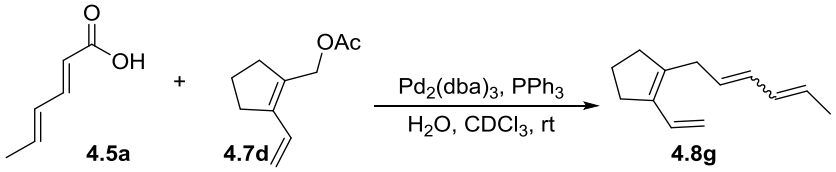
1H), 2.94 – 2.88 (m, 1H), 2.44 – 2.35 (m, 1H), 2.34 – 2.25 (m, 1H), 1.87 (ddt, J_t = 12.6, J_d = 7.5, J_d = 4.5 Hz, 1H), 1.74 (d, J = 6.5 Hz, 3H), 1.56 – 1.47 (m, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ 143.0, 134.3, 132.7, 131.5, 130.3, 129.6, 128.1, 111.2, 38.5, 29.5, 28.8, 18.3 ppm.

HRMS (APPI) calcd. for $[C_{12}H_{16}]^+$: 160.1246, found: 160.1245.







1-(hexa-2,4-dien-1-yl)-2-vinylcyclopent-1-ene, 4.8g

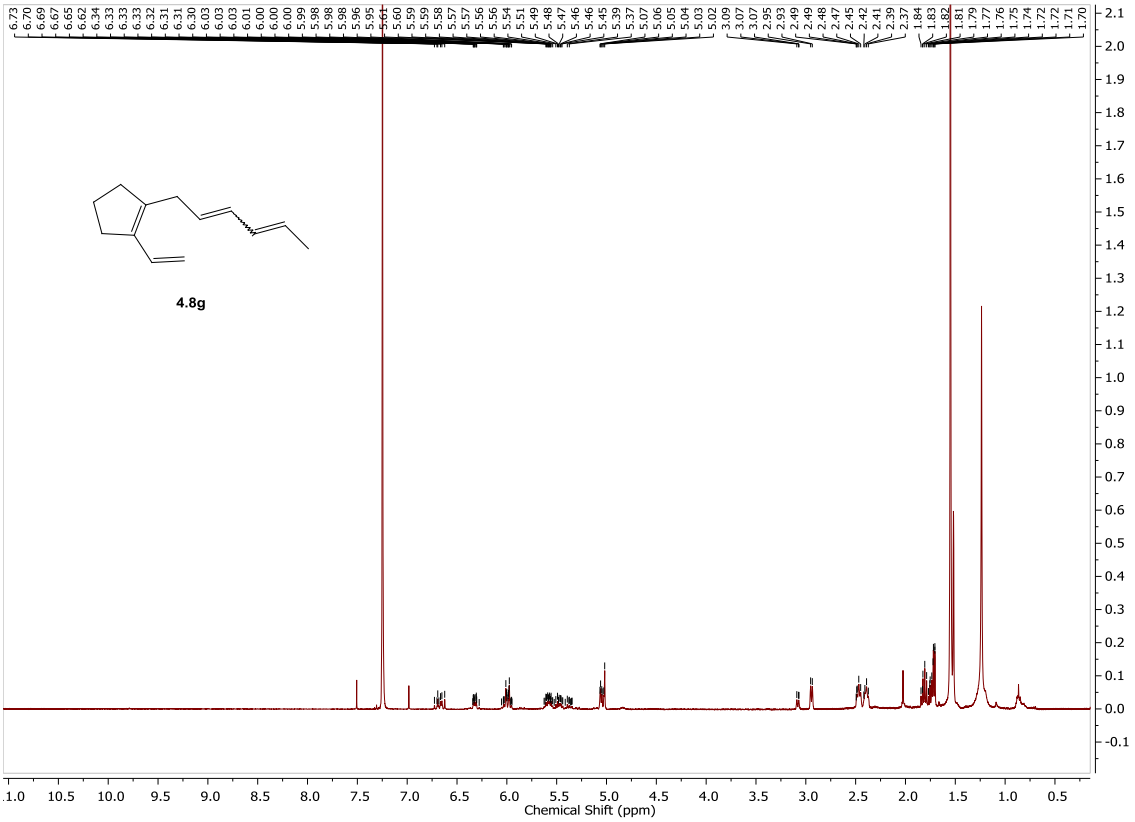
Following the general procedure, tetraene **4.8g** was synthesized as a colorless oil, (2.0 mg, 18%). R_f = 0.96 (90:10, hexanes/EtOAc). The product is a mixture of two diastereomers in a 2:1 ratio. Only the major diastereomer was fully characterized.

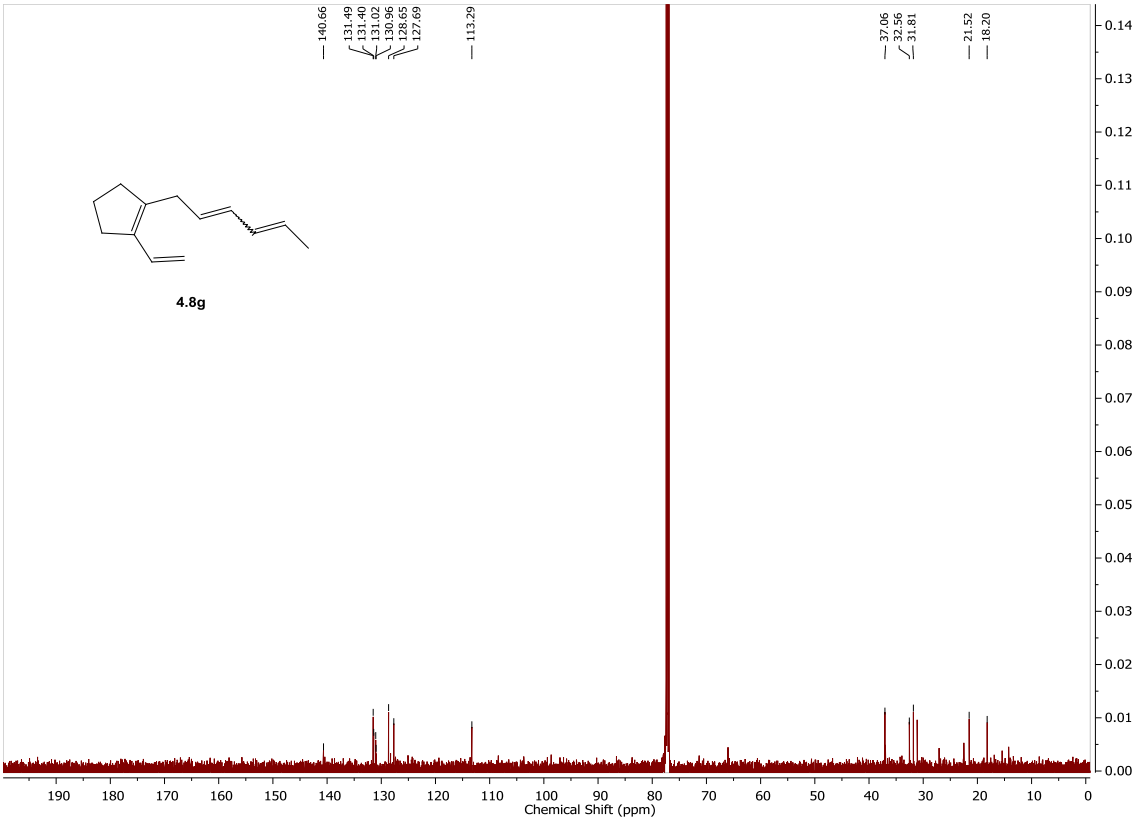
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.67 (dd, *J* = 16.8, 11.0 Hz, 1H), 6.06 – 5.95 (m, 2H), 5.63 – 5.55 (m, 1H), 5.53 – 5.45 (m, 1H), 5.09 – 5.02 (m, 2H), 2.96 (d, *J* = 6.9 Hz, 2H),

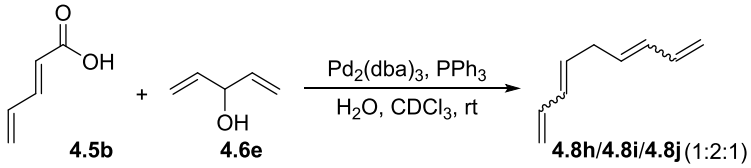
2.50 – 2.47 (m, 2H), 2.42 – 2.39 (m, 2H), 1.85 – 1.79 (m, 2H), 1.72 (d, J = 6.5 Hz, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ 140.7, 131.5, 131.4, 131.0, 130.9, 128.7, 127.7, 113.3, 37.1, 32.6, 31.8, 21.5, 18.2 ppm.

HRMS (APPI) calcd. for $[C_{13}H_{18}+H]^+$: 175.1487, found: 175.1480.







Nona-1,3,6,8-tetraene, 4.8h/4.8i/4.8j

Following the general procedure, tetraenes **4.8h/4.8i/4.8j** were synthesized as a colorless solution in $CDCl_3$ (14% ^{1}H NMR yield). R_f = 0.73 (hexanes).

Mixture of three inseparable diastereomers (*E*/*E*, *E*/*Z*, *Z*/*Z*)

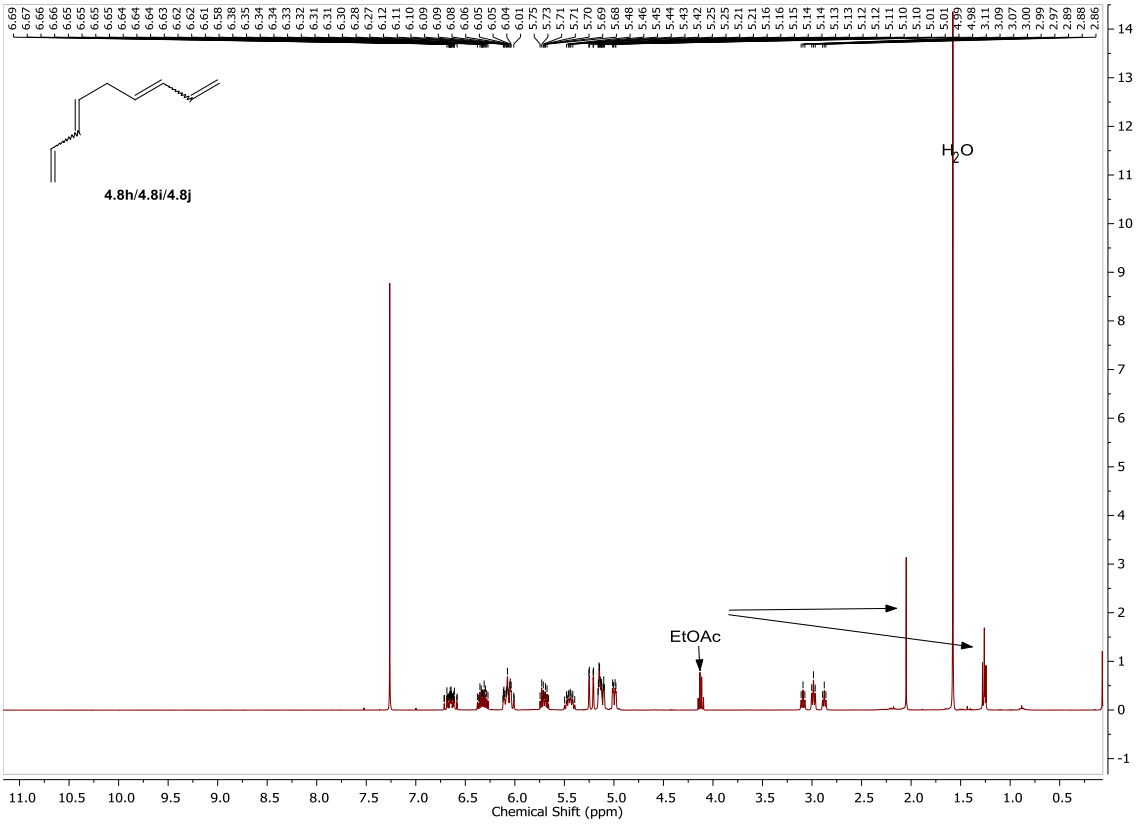
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.71 – 6.58 (m, 1H), 6.38 – 6.27 (m, 1H), 6.13 – 6.00 (m, 2H), 5.70 (dq, J_d = 15.3 Hz, J_q = 6.4 Hz, 1H), 5.50 – 5.40 (m, 1H), 5.23 (dd, *J* = 16.9, 1.6 Hz, 1H), 5.15 – 5.1 (m, 2H), 4.99 (dd, *J* = 10.0, 3.3 Hz, 1H), 3.09 (t, *J* = 7.6 Hz, 0.53H

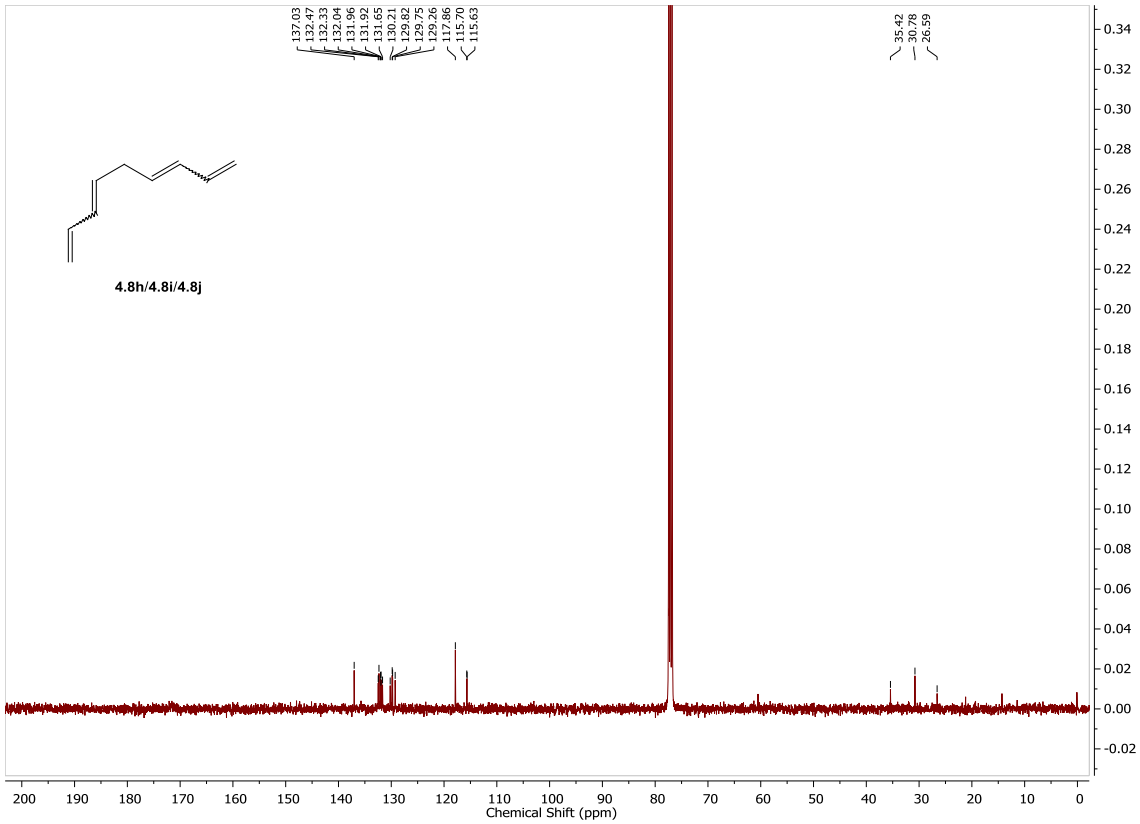
diastereomer **4.8h**), 2.99 (t, *J* = 7.1 Hz, 0.99H *diastereomer* **4.8i**), 2.99 (t, *J* = 6.7 Hz, 0.60H *diastereomer* **4.8j**) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 137.0, 132.5, 132.3, 132.1, 132.0, 131.9, 131.6, 130.2, 129.8, 129.8, 129.3, 117.8, 115.7, 115.6, 35.4, 30.7, 26.6 ppm.

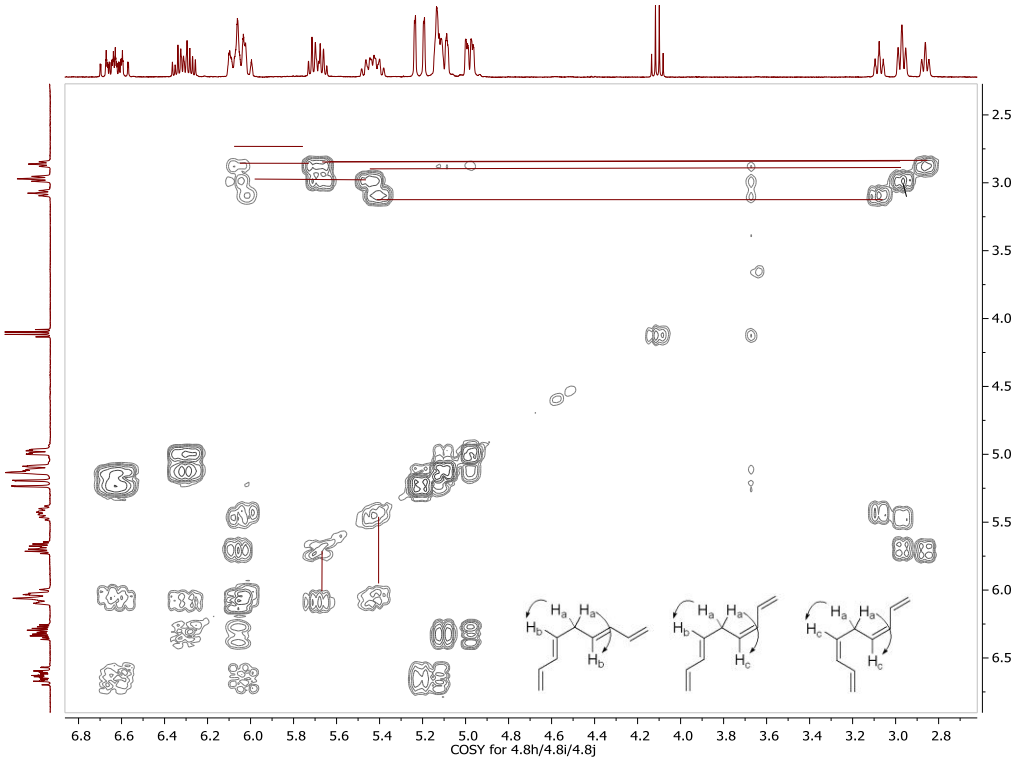
GC-LR-MS (EI 70 eV) m/z (%) calcd. for C_9H_{12}: 120, found: 120.

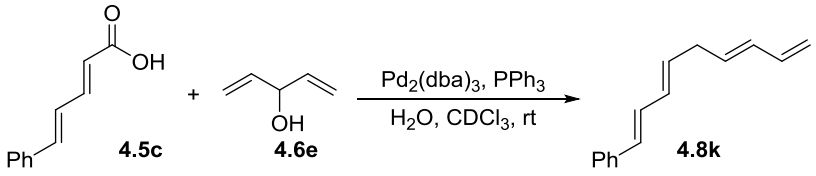
Attempts to obtain HRMS data using ESI and API were unsuccessful.




137.03
132.47
132.33
132.04
131.96
131.92
131.65
130.21
129.82
129.75
129.26
117.86
115.70
115.63
35.42
30.78
26.59
4.8h/4.8i/4.8j
Chemical Shift (ppm)

COSY for 4.8h/4.8i/4.8j





((1*E*,3*E*,6*E*)-nona-1,3,6,8-tetraen-1-yl)benzene, 4.8k

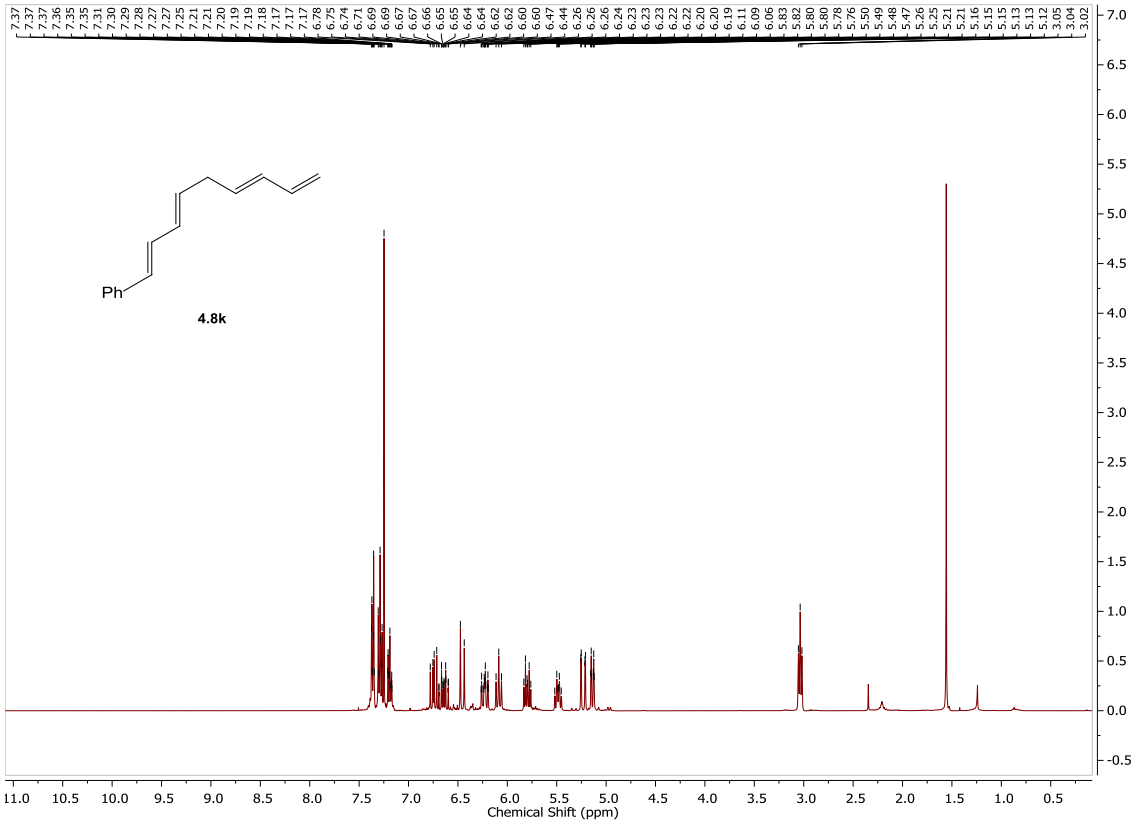
Following the general procedure, tetraene **4.8k** was synthesized as a yellow oil (8.2 mg, 24% yield). R_f = 0.62 (hexanes).

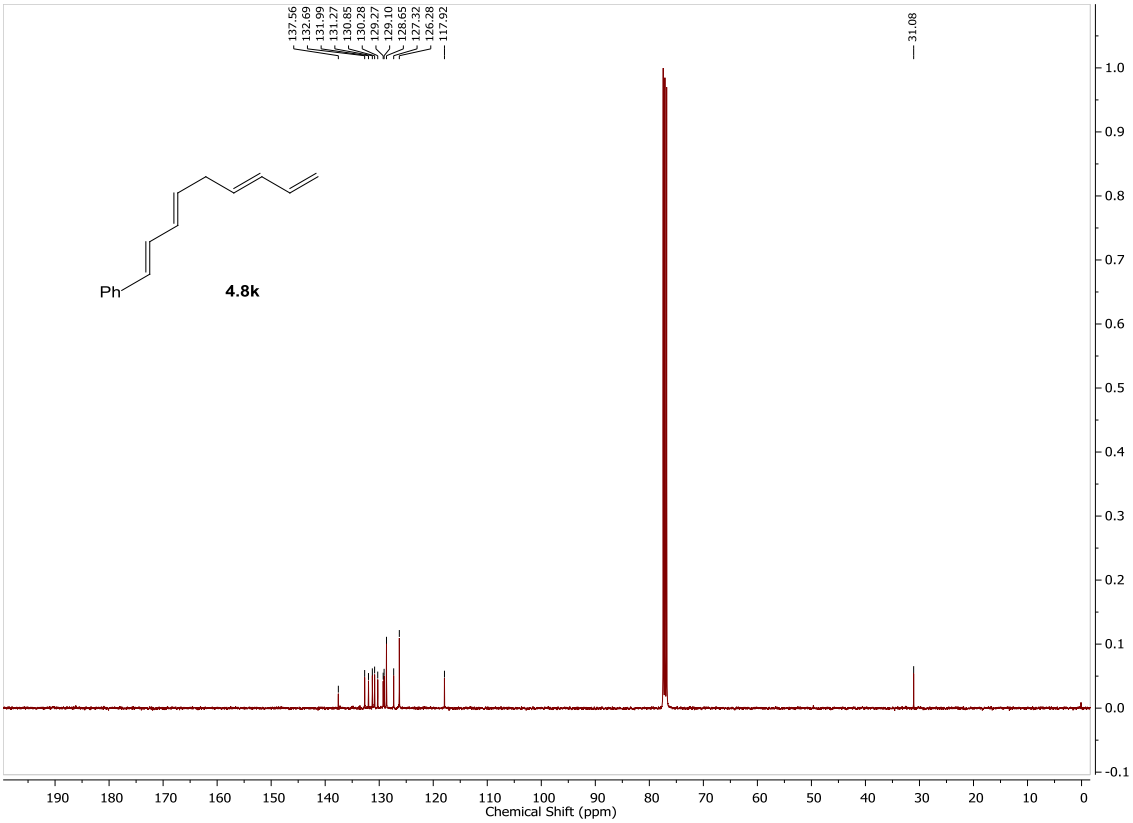
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.35 (m, 2H), 7.29 (dt, J_d = 8.6 Hz, J_t = 6.8 Hz, 2H), 7.19 (tt, J = 6.4, 1.2 Hz, 1H), 6.75 (dd, J = 15.6, 10.5 Hz, 1H), 6.64 (dtd, J_d = 16.9, 1.0 Hz, J_t = 10.6 Hz, 1H), 6.45 (d, J = 12.0 Hz, 1H), 6.23 (ddt, J_d = 14.0, 10.4 Hz, J_t = 1.7, 1H), 6.09 (t, J = 11 Hz, 1H), 5.80 (dt, J_d = 15.0 Hz, J_t = 6.6 Hz 1H), 5.49 (dt, J_d =

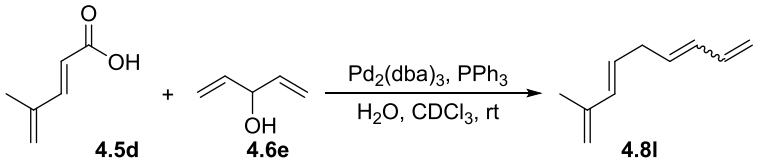
10.7 Hz, J_t = 7.9 Hz, 1H), 5.23 (dd, J = 16.9, 1.6 Hz, 1H), 5.14 (td, J_d = 10.4, J_t = 1.9 Hz, 1H), 3.04 (t, J = 7.1 Hz, 2H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 137.6, 132.7, 132.0, 131.3, 130.8, 130.3, 129.3, 129.1, 128.6 (2C), 127.3, 126.2 (2C), 117.9, 31.1 ppm.

HRMS (APPI) calcd. for $[C_{15}H_{16} + H]^+$: 197.1330, found: 197.1323.







(3*E*,6*E*)-2-methylnona-1,3,6,8-tetraene, 4.8l

Following the general procedure, tetraene **4.8l** was synthesized as a colorless liquid (36% ^{1}H NMR yield). R_f = 0.69 (hexanes). The product is a mixture of two diastereomers in a 4:1 ratio.

Mixture of two inseparable diastereomers:

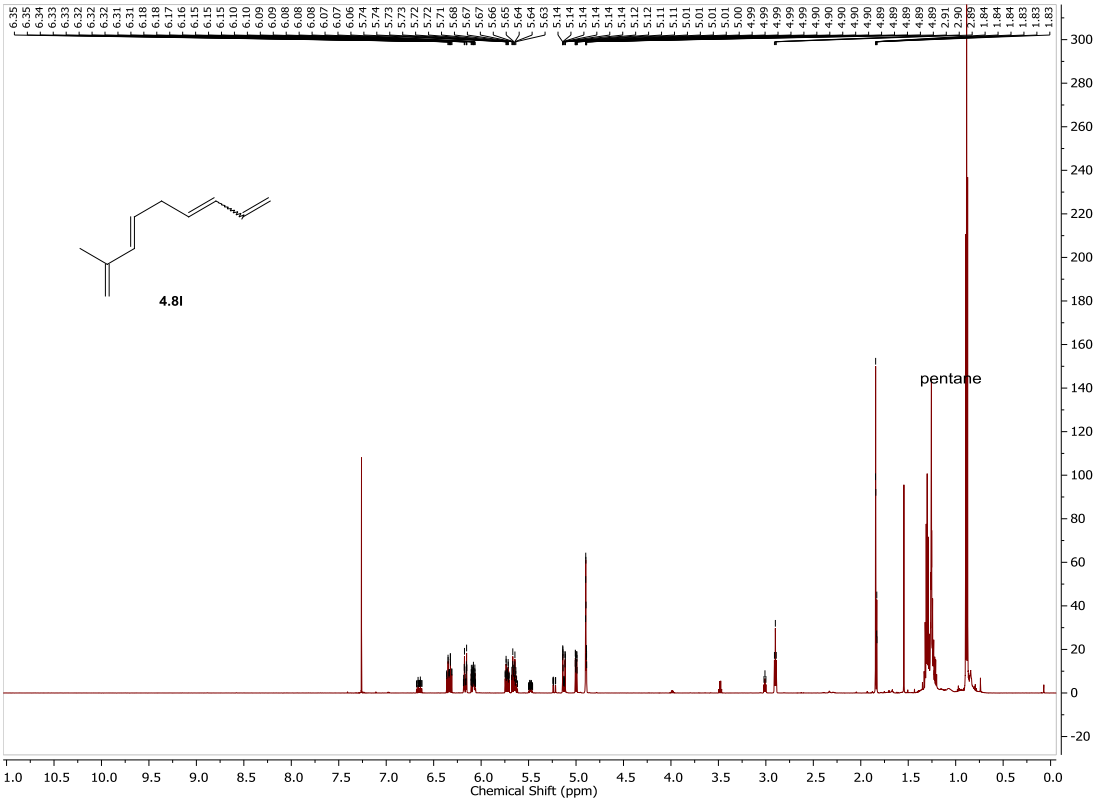
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.65 (dddd, *J* = 16.8, 11.2, 10.2, 1.1 Hz, 1H, *minor isomer*), 6.34 (dtd, J_d = 17.0, 0.7 Hz, J_t = 10.2 Hz, 1H, *major isomer*), 6.21 – 6.12 (m,

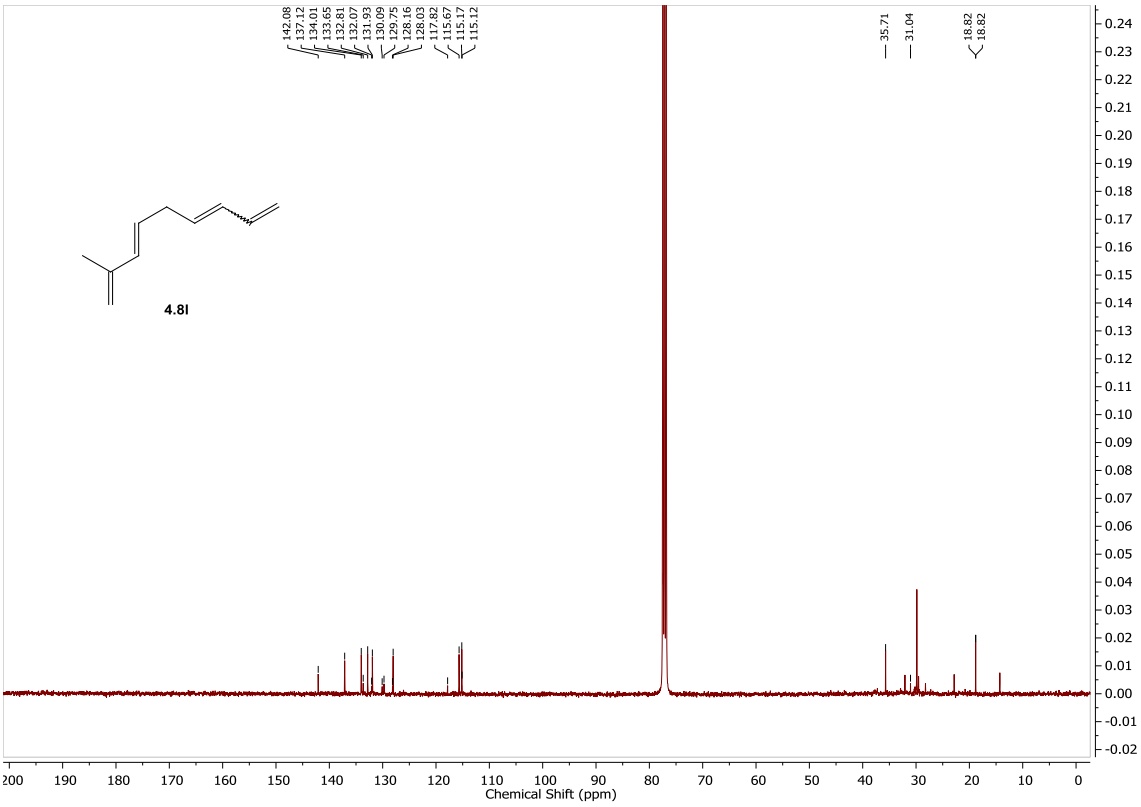
1H), 6.12 – 6.01 (m, 1H), 5.73 (dtd, J_d = 15.2, 0.7 Hz, J_t = 6.8 Hz, 1H), 5.68 – 5.58 (m, 1H), 5.52 – 5.42 (m, 1H, *minor isomer*), 5.25 – 5.21 (m, 1H, *minor isomer*), 5.15 – 5.11 (m, 1H), 5.00 (ddd, *J* = 10.3, 1.6, 0.9 Hz, 1H), 4.90 – 4.88 (m, 2H), 3.01 (t, *J* = 7.1 Hz, 2H, *CH_2 minor isomer*), 2.90 (t, *J* = 6.7 Hz, 2H, CH_2 *major isomer*), 1.84 (t, *J* = 1.0 Hz, 3H, CH_3 *major isomer*), 1.83 (t, *J* = 1.0 Hz, 1H, CH_3 *minor isomer*) ppm.

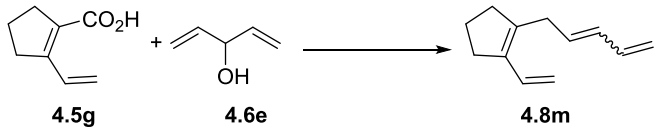
^{13}C NMR (125 MHz, $CDCl_3$) δ 142.1, 137.1, 134.0, 133.6, 132.8, 132.1, 131.9, 130.1, 129.7, 128.2, 128.0, 115.6, 115.2, 115.1, 35.7, 29.8, 18.8 ppm.

GC-LR-MS (EI 70 eV) m/z (%) calcd. for $C_{10}H_{14}$: 134, found: 134.

Attempts to obtain HRMS data using ESI and API were unsuccessful.







4.5g **4.6e** **4.8m**

(*E*,*Z*)-1(penta-2,4-dien-1-yl)-2-vinylcyclopent-1-ene, 4.8m

See Chapter III-section 4.3, page 116 compound **3.29** for experimental details,

5. References

1. Torborg, C.; Beller, M. *Adv. Synth. Catal.* **2009,** *351*, 3027–3043.

2. McGlacken, G. P.; Fairlamb, I. J. S. *Eur. J. Org. Chem.* **2009,** *2009*, 4011–4029.

3. Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem. Int. Ed.* **2005,** *44*, 4442–4489.

4. Terao, J.; Kambe, N. *Acc. Chem. Res.* **2008,** *41*, 1545–1554.

5. Martin, R.; Buchwald, S. L. *Acc. Chem. Res.* **2008,** *41*, 1461–1473.

6. Marion, N.; Nolan, S. P. *Acc. Chem. Res.* **2008,** *41*, 1440–1449.

7. Denmark, S. E.; Regens, C. S. *Acc. Chem. Res.* **2008,** *41*, 1486–1499.

8. Kantchev, E. A. B.; O'Brien, C. J.; Organ, M. G. *Angew. Chem. Int. Ed.* **2007,** *46*, 2768–2813.

9. Corbet, J.-P.; Mignani, G. *Chem. Rev.* **2006,** *106*, 2651–2710.

10. Schaub, T. A.; Kivala, M., Cross-Coupling Reactions to sp Carbon Atoms. In *Metal-Catalyzed Cross-Coupling Reactions and More*, Wiley-VCH Verlag GmbH & Co. KGaA: 2014; pp 665.

11. Davies, H. M. L.; Morton, D. *J. Org. Chem.* **2016,** *81*, 343–350.

12. Brückl, T.; Baxter, R. D.; Ishihara, Y.; Baran, P. S. *Acc. Chem. Res.* **2012,** *45*, 826–839.

13. Stuart, D. R.; Fagnou, K., The Discovery and Development of a Palladium(II)-Catalyzed Oxidative Cross-Coupling of Two Unactivated Arenes. In *Inventing Reactions*, Gooßen, L. J., Ed. Springer Berlin Heidelberg: Berlin, Heidelberg, 2013; pp 91.

14. Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010,** *110*, 624–655.

15. Campeau, L.-C.; Rousseaux, S.; Fagnou, K. *J. Am. Chem. Soc.* **2005,** *127*, 18020–18021.

16. Stuart, D. R.; Alsabeh, P.; Kuhn, M.; Fagnou, K. *J. Am. Chem. Soc.* **2010,** *132*, 18326–18339.

17. Gorelsky, S. I.; Lapointe, D.; Fagnou, K. *J. Org. Chem.* **2012,** *77*, 658–668.

18. Lafrance, M.; Fagnou, K. *J. Am. Chem. Soc.* **2006,** *128*, 16496–16497.

19. Tsuda, T.; Chujo, Y.; Nishi, S.; Tawara, K.; Saegusa, T. *J. Am. Chem. Soc.* **1980,** *102*, 6381–6384.

20. Tsuda, T.; Okada, M.; Nishi, S.; Saegusa, T. *J. Org. Chem.* **1986,** *51*, 421–426.

21. Trost, B. M.; Bunt, R. C. J. Am. Chem. Soc. 1998, 120, 70–79.

22. Corey, E. J.; Fraenkel, G. *J. Am. Chem. Soc.* **1953,** *75*, 1168–1172.

23. Waetzig, S. R.; Rayabarapu, D. K.; Weaver, J. D.; Tunge, J. A. *Angew. Chem. Int. Ed.* **2006,** *45*, 4977–4980.

24. Waetzig, S. R.; Tunge, J. A. *J. Am. Chem. Soc.* **2007,** *129*, 14860–14861.

25. Grenning, A. J.; Tunge, J. A. *Org. Lett.* **2010,** *12*, 740–742.

26. Rayabarapu, D. K.; Tunge, J. A. *J. Am. Chem. Soc.* **2005,** *127*, 13510–13511.

27. Sim, S. H.; Park, H.-J.; Lee, S. I.; Chung, Y. K. *Org. Lett.* **2008,** *10*, 433–436.

28. Pi, S.-F.; Tang, B.-X.; Li, J.-H.; Liu, Y.-L.; Liang, Y. *Org. Lett.* **2009,** *11*, 2309–2312.

29. Torregrosa, R. R. P.; Ariyarathna, Y.; Chattopadhyay, K.; Tunge, J. A. *J. Am. Chem. Soc.* **2010,** *132*, 9280–9282.

30. Zhang, W.-W.; Zhang, X.-G.; Li, J.-H. *J. Org. Chem.* **2010,** *75*, 5259–5264.

31. Rodriguez, N.; Goossen, L. J. *Chem. Soc. Rev.* **2011,** *40*, 5030–5048.

32. Gooßen, L. J.; Deng, G.; Levy, L. M. *Science* **2006,** *313*, 662–664.

33. Gruber, S.; Zaitsev, A. B.; Wörle, M.; Pregosin, P. S.; Veiros, L. F. *Organometallics* **2008,** *27*, 3796–3805.

34. Yamashita, M.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2010,** *12*, 592–595.

35. Patel, B. A.; Dickerson, J. E.; Heck, R. F. *J. Org. Chem.* **1978,** *43*, 5018–5020.

36. Yamashita, M.; Hirano, K.; Satoh, T.; Miura, M. *Adv. Synth. Catal.* **2011,** *353*, 631–636.

37. Yamashita, M.; Hirano, K.; Satoh, T.; Miura, M. *Chem. Lett.* **2010,** *39*, 68–69.

38. Abu Deiab, G. I.; Croatt, M. P., Chapter 3 - Step-Economical Synthesis of Clinprost and Analogs Utilizing a Novel Decarboxylation Reaction. In *Strategies and Tactics in Organic Synthesis*, Michael, H., Ed. Academic Press, 2017; Vol. 12, pp 95–117.

39. Nagy, E. E.; Hyatt, I. F. D.; Gettys, K. E.; Yeazell, S. T.; Frempong, S. K.; Croatt, M. P. *Org. Lett.* **2013,** *15*, 586–589.

40. Hettrick, C. M.; Kling, J. K.; Scott, W. J. *J. Org. Chem.* **1991,** *56*, 1489–1492.

41. Gradén, H.; Hallberg, J.; Kann, N.; Olsson, T. *J. Combin. Chem.* **2004,** *6*, 783–788.

42. Surovtseva, D. A.; Orlov, D. A.; Morozova, T. A.; Krylov, A. V.; Belov, A. P. *Kin. Catal.* **2006,** *47*, 855–860.

43. Alfonso, D. R.; Jordan, K. D. *J. Combin. Chem.* **2003,** *24*, 990–999.

44. Marcus, A. P.; Lee, A. S.; Davis, R. L.; Tantillo, D. J.; Sarpong, R. *Angew. Chem. Int. Ed.* **2008,** *47*, 6379–6383.

45. Nilsson, Y. I. M.; Andersson, P. G.; Baeckvall, J. E. *J. Am. Chem. Soc.* **1993,** *115*, 6609–6613.

46. Mutlu, H.; Ruiz, J.; Solleder, S. C.; Meier, M. A. R. *Green Chem.* **2012,** *14*, 1728–1735.

47. Bosque, I.; Bagdatli, E.; Foubelo, F.; Gonzalez-Gomez, J. C. *J. Org. Chem.* **2014,** *79*, 1796–1804.

48. Garza, V. J.; Krische, M. J. *J. Am. Chem. Soc.* **2016,** *138*, 3655–3658.

49. Tabuchi, T.; Inanaga, J.; Yamaguchi, M. *Tetrahedron lett.* **1986,** *27*, 601–602.

50. Harding, K. E.; Strickland, J. B.; Pommerville, J. *J. Org. Chem.* **1988,** *53*, 4877–4883.

CHAPTER V

CONCLUSION

Isocarbacyclin and its analogues play an important role in treating neuronal damage following an ischemic stroke which makes the synthesis of new analogues important. The enantioselective total synthesis of isocarbacyclin is described herein using only 9 steps from inexpensive, commercially available materials. Three metal-catalyzed reactions including Pd^{0}-catalyzed decarboxylation, Rh^{I}-catalyzed cycloaddition and Ru^{II}-catalyzed cross metathesis were utilized in this synthesis. Other analogues were synthesized by attaching different ω-sidechains in a late-stage to shorten the synthesis to 7-8 steps. Isocarbacyclin and its analogues were sent to a research lab that studies ischemic stroke to test their neuroprotective activity.

Another generation of isocarbacyclin analogues was developed to increase the yield of the cycloaddition step compared to isocarbacyclin synthesis. A model system worked successfully for this generation where the three metal-catalyzed reactions that were used in the synthesis of isocarbacyclin were tested. However, efforts toward the cycloaddition step resulted in a different type of reaction. For future analogues of this type, the carboxyl group will be revealed at a late stage in the synthesis.

The decarboxylation coupling reaction of pentadienyl dienoate that was discovered in the synthesis of isocarbacyclin and its analogues was studied in more detail. Different conditions were screened to optimize the reaction. It was found that both

pentadienyl and dienoate groups are required for the decarboxylative coupling reaction. The decarboxylative coupling was found to work at ambient temperature and without the need of an anion-stabilizing group. Other different conditions were screened to study the mechanism, which was studied more in detail by computational studies. Having the reaction optimized, different 1,3,6,8-tetraenes were synthesized using this type of reaction.